TITLE OF THE INVENTION: Method for the screening of $\alpha_2\delta$-1 subunit binding ligands

This application is a Continuation of USSN 09/397,549 filed September 16, 1999; the entire contents of which are herein incorporated by reference.

FIELD OF THE INVENTION

The invention relates to a method for the screening of ligands which bind a soluble secreted cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-1 subunit polypeptide.

BACKGROUND OF THE INVENTION

Gabapentin (1-aminoethyl-cyclohexane acetic acid) is currently commercialized for the treatment of epilepsy. The compound has however been recognized as being also useful for the treatment of pain and anxiety.

Recent reports have suggested an interaction between gabapentin and the $\alpha_2\delta$ subunit of a voltage-dependent calcium channel (VDCC). But electro-physiological studies have yielded conflicting data on the action of gabapentin at VDCCs, even though the relevance of the interaction of gabapentin at the $\alpha_2\delta$ subunit to the clinical utility of the drug is becoming clearer. However, none of the prototype anticonvulsant drugs displace [^{3}H]gabapentin binding from the $\alpha_2\delta$-1 subunit.

The most frequently used assay currently available for the screening of ligands that bind the $\alpha_2\delta$ subunit involves the use of pig membrane extracts as a source of the $\alpha_2\delta$ subunit. Such an assay presents major inconvenience. Firstly, because the assay material is a membrane extract, it is very difficult to accurately determine the protein composition from one assay preparation to another particularly with regard to the subtype. Also, the presence of various impurities in the assay preparation is a problem in small plate assays. Furthermore, as the protein preparation lacks homogeneity, the interaction between the targeted protein and the assay plate is often quite uneven. This renders the streamlining of the assay in a high throughput format almost impossible to achieve.

SUMMARY OF THE INVENTION

The inventors have found that it was possible to use a soluble secreted form of a voltage-dependant calcium channel $\alpha_2\delta$-1 subunit polypeptide (hereinafter $\alpha_2\delta$-1 subunit polypeptide) in an assay for the screening of ligands which bind the $\alpha_2\delta$-1 subunit.

The exact position and configuration of the [^{3}H]gabapentin binding site on the $\alpha_2\delta$ subunit is not currently known. Furthermore, recent deletion experiments on the porcine $\alpha_2\delta$-1 subunit coding sequence have shown that amino-acids close to the C-terminal region are needed in order for the protein to bind [^{3}H]gabapentin. For this very reason, the use of truncated forms of the porcine $\alpha_2\delta$-1 subunit in screening assays has not been disclosed or suggested in the prior art because there was concern as to whether relevant levels of binding capacity would be achieved in an assay environment.

The assay of the invention is of considerable interest because it confirms that a recombinant soluble secreted $\alpha_2\delta$-1 subunit polypeptide can be used in high throughput $\alpha_2\delta$-1 ligand screening. It also provides a useful advantage over the pig membrane extract screening assay as it allows the study of $\alpha_2\delta$-1 subtype-specific binding ligands. Proteins can be tagged which makes purifying convenient and possible to use a tagged antibody for recognition.

It was not clear whether the addition of the 6His tag to the C-terminus of the protein would affect the [^{3}H]gabapentin binding properties of $\alpha_2\delta$

It was also unclear whether a C-terminally located 6His tag on $\alpha_2\delta$ would be accessible for interaction with the Ni NTA chromatography matrix (for purification purposes) and SPA bead, or Ni flashplate well surface (for purposes of the assay).

The invention concerns a method for the screening of ligands which bind a calcium channel $\alpha_2\delta$-1 subunit.

The method comprises the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide with:

- a ligand of interest; and
- a labelled compound which binds a $\alpha_2\delta$-1 subunit; and

- measuring the level of binding of the labelled compound to the secreted soluble $\alpha_2\delta$-1 subunit.

The invention also concerns a kit for the screening of ligands which bind a calcium channel $\alpha_2\delta$-1 subunit.

The kit comprises:

- a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide; and
- a labelled compound which binds a calcium channel $\alpha_2\delta$-1 subunit.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 represents the elution profile of the recombinant polypeptide with the amino acid sequence of SEQ ID No 9 purified by Superdex-200 chromatography, either before or after electron on NI-NTA.

Figure 2 illustrates the optimization of imidazole concentrations in an embodiment of the SPA assay of the invention.

Figure 3 illustrates the optimization of imidazole concentrations in an embodiment of the flashplate assay of the invention.

Figure 4 illustrates the flashplate time course of [^{3}H]gabapentin binding to various concentrations of the recombinant polypeptide with the amino acid sequence of SEQ ID No 9.

Figure 5 illustrates the capacity of the recombinant polypeptide with the amino acid sequence of SEQ ID No 9 in a flashplate assay after 3 hours of incubation.

Utility Application

Figure 6 illustrates the optimum imidazole concentration, assayed after 3 hours of incubation, required to maximize [^{3}H]gabapentin binding using a constant amount of the recombinant polypeptide with the amino acid sequence of SEQ ID No 9.

Figure 7 illustrates flashplate assay of [^{3}H]gabapentin saturation binding to the purified recombinant polypeptide with the amino acid sequence of SEQ ID No 9, assayed after 3 hours of incubation.

Figure 8 illustrates the flashplate time course optimisation of imidazole concentration required to maximize the [^{3}H]Leucine binding window to to the purified recombinant polypeptide with the amino acid sequence of SEQ ID No 9, assayed after 3 hours of incubation.

Figure 9 illustrates competition curves of three compounds in the flashplate assay format, assayed after 3 hours of incubation.

DETAILED DESCRIPTION OF THE INVENTION

The invention concerns a method for the screening of ligands which bind a soluble secreted $\alpha_2\delta$-1 subunit polypeptide. The term $\alpha_2\delta$-1 subunit polypeptide, when used herein, is intended to designate a structure containing two polypeptides (α_2 and δ) attached to one another by covalent desulfide bridges. More particularly, the targeted $\alpha_2\delta$-1 subunit binding site is preferably the [^{3}H]gabapentin binding site. The various parameters of the method of the invention are described in further detail below.

A – Secreted soluble recombinant $\alpha_2\delta$-1 subunit polypeptide

Several nucleotide sequences encoding a secreted soluble form of an $\alpha_2\delta$-1 subunit can be used in the context of the present invention. Preferred soluble secreted $\alpha_2\delta$-1 subunit polypeptides are derived from eukaryotic $\alpha_2\delta$-1 subunits, more preferably from mammal, such as mouse, rat, rabbit, porcine, bovine or others and human $\alpha_2\delta$-1 subunits. Most preferred soluble secreted $\alpha_2\delta$-1 subunit polypeptides are derived from the human or porcine $\alpha_2\delta$-1 subunits.

More specifically, the selected nucleotide sequences encode a secreted soluble polypeptide having at least 80%, preferably 90%, more preferably 95%, and most preferably 98 or 99% amino-acid identity with the polypeptide comprising from amino acid 1 to between amino-acids 985 and 1054, preferably between amino-acids 985 and 1059, and most preferably between amino-acids 1019 and 1044 of SEQ ID NO:5 or SEQ ID NO:16.

In order to determine the optimal deletions on the $\alpha_2\delta$-1 subunit cDNA that yield a soluble secreted polypeptide devoid of membrane anchorage structures and having a functional [^{3}H]gabapentin binding site, the inventors tested the expression of several human or porcine $\alpha_2\delta$-1 subunit cDNA deletion mutants. The discussion provided below provides detailed comments on possible truncations, giving as an example the porcine $\alpha_2\delta$-1 subunit. However, given the very substantial cross-species homology for $\alpha_2\delta$-1 subunit sequences, the comments below can also be applied o other eukaryotic species, and more particularly other mammation species such as the rat, the mouse or the rabbit. Their $\alpha_2\delta$-1 subunit sequences, which are available in public databases, share a very substantial homology with the human and porcine $\alpha_2\delta$-1 subunit sequences.

The inventors found that by deleting from the porcine $\alpha_2\delta$-1 subunit cDNA a nucleotide sequence encoding as much as amino-acids 967 to 1091 of the native protein, soluble polypeptides could be obtained. On the other hand, the minimal deletion required to achieve solubility appears to be located around nucleotides encoding amino-acids 1064 to 1091 of the sequence of SEQ ID NO:5. In this regard, the mutant polypeptide expressed using a cDNA deletion mutant from which a sequence encoding amino-acids 1064 to 1091 is removed is found in both soluble and membrane-associated forms, with [^{3}H]gabapentin and/or other derivatives or compounds such as pregabalin and gabapentoids binding properties similar to that of the wild type protein. Furthermore, a mutant protein expressed using a cDNA deletion mutant from which a nucleotide sequence encoding amino-acids 1085 to 1091 is removed recovers its membrane anchorage properties. Also, mutant proteins expressed using cDNA deletion mutants from which nucleotide sequences encoding either amino-acids 1037 to 1091 or amino-acids 1019 to 1091 of SEQ ID NO:5 or 16 are removed are found in soluble form.

The inventors believe that the soluble secreted $\alpha_2\delta$-1 subunit polypeptides which are as close as possible to the native sequence and which are therefore more likely to retain their native folding and hence their [^{3}H]gabapentin- binding properties are those corresponding to a protein in which amino-acid stretch 985-1091 to 1074-1091, the amino-acid sequence of SEQ ID NO:5 or 16 has been deleted. The skilled scientist can quite easily determine within this amino-acid stretch the optimal mutant protein.

The invention therefore particularly concerns a screening assay in which the secreted soluble $\alpha_2\delta$-1 subunit polypeptide is preferably a polypeptide having at least 80% identity with the polypeptide comprising from amino-acid 1 to between amino-acid 985 and 1054, preferably between amino-acids 985 and 1059, and most preferably between amino-acids 1019 and 1064 of SEQ ID NO:5 or SEQ ID NO:16.Preferred $\alpha_2\delta$-1 subunit polypeptides which can be used in the present invention are those of SEQ ID N°6, 7, 8, 9, 13, 14 and 15, with the polypeptides of SEQ ID NO:9 or SEQ ID NO:15 being most preferred.

In a first and preferred embodiment of the invention, the $\alpha_2\delta$-1 subunit polypeptide is purified before it is used in the assay. The purification step, an example of which is provided further in this specification, can be carried out using several purification techniques well-known to the skilled person.

In some instances, it is required to tag the $\alpha_2\delta$-1 subunit polypeptide prior to purification. The tag is then in most instances encoded into the nucleotide sequence that is needed to express the polypeptide. Examples of such tags include, but are not limited to sequences encoding C-myc, FLAG, a sequence of histidine residues, heamaglutin A, V5, Xpress or GST. Most of these tags can be incorporated directly into the sequence, for instance through PCR amplification by incorporating the appropriate coding sequence in one of the PCR amplification primers. However, the tag can also be introduced by other means such as covalent binding of the appropriate nucleic acid sequence encoding the tag moiety with the 5' or 3' end of the nucleic acid sequence encoding the polypeptide sequence. This is the

case for GST. It should be noted that the tag can be located at either end of the polypeptide sequence. Furthermore, in some instances, it can be advantageous to insert a cleavage site between the tag and the polypeptide sequence in order to permit removal of the tag sequence if needed.

In other cases, providing a tag to the polypeptide is not needed. For instance, the protein can be purified using affinity columns loaded with specific monoclonal antibodies.

In a second embodiment of the invention, the $\alpha_2\delta$-1 subunit polypeptide can be only partially purified. For instance, it can be purified along with other contaminating proteins using an appropriate chromatography matrix such as ion-exchange chromatography column. In such instances, it is not required to tag the desired polypeptide of interest.

The most preferred embodiment contemplated by the inventors concerns the use of a purified tagged $\alpha_2\delta$-1 subunit polypeptide. A particularly preferred tag is a nucleotide sequence encoding from 2 to 10, and preferably 6 histidine residues as provided in the polypeptide of SEQ ID No 9.

With regard to the $\alpha_2\delta$-1 subunit polypeptide used subsequently in the screening assay of the invention, several possibilities are also open to the skilled person.

In a first and preferred embodiment, the $\alpha_2\delta$-1 subunit polypeptide comprises a tag moiety which can be selected among the tags referred to above. Such tagged polypeptides are particularly useful in SPA or flashplate assays. A preferred tag is the nucleotide sequence encoding histidine residues referred to above.

In a second embodiment, the $\alpha_2\delta$-1 subunit polypeptide can be used without a tag. This is the case for instance in SPA or flashplate assays comprising beads or plates coated with wheat germ lectin. In such an embodiment, the tag is not needed as the carbohydrate moieties of the $\alpha_2\delta$-1 subunit polypeptide bind directly to the wheat germ lectin-coated beads or plates.

B - Labelled compounds which bind the $\alpha_2\delta$-1 subunit polypeptide

In cases where the $\alpha_2\delta$-1 binding site is the [^{3}H]gabapentin binding site, the preferred labelled compound which can be used is of course gabapentin itself. However, gabapentin is not the only labelled compound which can be used in this context. Indeed, it has been previously demonstrated that saturation binding analyses on porcine synaptic plasma cerebral cortex membranes performed in the presence of L-leucine indicate a competitive interaction of the amino acid with the [^{3}H]gabapentin binding site, significantly reducing [^{3}H]gabapentin binding affinity for the site. The inventors believe that this competitive interaction is true across across all the amino-acids listed in table 1 below.

Table 1

Binding affinities of selected amino acids (IC_{50} <500nM) for the [^{3}H]gabapentin site in porcine cortical membranes

COMPOUND	IC_{50} (NM) ARITHMETIC MEAN (N=3) ± S.E.M.
Gabapentin	42.1 ± 5.5
L-Norleucine	23.6 ± 6.7
L-Allo-Isoleucine	32.8 ± 6.0
L-Methionine	49.6 ± 10.0
L-Leucine	61.3 ± 20.9
L-Isoleucine	68.8 ± 1.9
L-Valine	330 ± 18
L-Phenylalanine	351 ± 89

It is therefore possible to use commercialy available labelled forms of these high affinity ligands in replacement of gabapentin. The utility of [^{3}H]L-leucine has been demonstrated in a filter binding assay and in a flashplate assay format. The inventors believe that labelled amino acids but also other compounds, with affinities preferably below 500 nM in the binding assay can be used as replacements of gabapentin.

With regard to the label, several embodiments can be used in the context of the invention. Preferred labels are of course radioactive labels, a list of which is provided further in this specification.

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C - Assay formats and conditions

Several assay formats can be used to carry out the method of the present invention. Preferred assay formats include scintillation assays such as the scintillation proximity assay (SPA) or the flashplate assay. Other assay formats well known to those skilled in the
10 arts such as the filter binding assay and the centrifugation assay are also contemplated in the present invention.

SPA and flashplate assays are preferred assay formats for the present invention. Additional details on these assays are provided below.

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Scintillation assay format

Scintillation assays technology either involves the use of scintillant beads (for the SPA assay) or plates (for the flashplate assay). SPA beads are usually made from either cerium-doped yttrium ion silicate (y2SiO5:Ce) or polyvinyltoluene (PVT) containing an organic
20 scintillant such as PPO. Flashplates commonly used are those such as Ni chelate flashplates although other flashplates can also be used.

Assays are usually carried out in aqueous buffers using radioisotopes such as ^{3}H, $^{125}1$, ^{14}c, ^{35}S or ^{33}P that emit low-energy radiation, the energy of which is easily dissipated in an
25 aqueous environment. For example, the electrons emitted b y ^{3} H have an average energy of only 6 keV and have a very short path length (-1 ~tm) in water. If a molecule labelled with one of these isotopes is bound to the bead or flashplate surface, either directly or via interaction with another molecule previously coupled to the bead or flashplate, the emitted radiation will activate the scintillant and produce light. The amount of light produced,
30 which is proportional to the amount of labelled molecules bound to the beads, can be measured conveniently with a liquid scintillation (LS) counter. If the labelled molecule is

not attached to the bead or a flashplate surface, its radiation energy is absorbed by the surrounding aqueous solvent before it reaches the bead, and no light is produced. Thus, bound ligands give a scintillation signal, but free ligands do not, and the need for a time-consuming separation step, characteristic of conventional radioligand binding assays, is eliminated. The manipulations required in the assays are reduced to a few simple pipetting steps leading to better precision and reproducibility.

The conditions under which SPA and flashplate assays are performed in the context of the present invention are provided below.

Scintillation assay conditions

1) SPA assay

The SPA assays is first developed to optimize the conditions under which the radioligand binds the $\alpha_2\delta$-1 subunit polypeptide. The parameters which can be varied to optimize radioligand binding in a typical SPA assay using Amersham beads include assay temperature, $\alpha_2\delta$-1 subunit polypeptide interaction with the radioligand and the SPA beads, radioligand concentration as well as pH variations.

The temperature at which the assay can be carried out can vary from 1 to 30°C. Preferred temperatures range from 18 to 23°C, with 21°C being the most preferred temperature. The interaction of the $\alpha_2\delta$-1 subunit polypeptide with the SPA beads can be optimized by adjusting the concentration of the polypeptide and by introducing a reagent which will favor this interaction. When 50 mg of Amersham SPA beads are used, the $\alpha_2\delta$-1 subunit polypeptide concentration may vary from 0.1 to 10 pmoles per well, with the optimal concentration being generally around 5 to 6 pmoles per well.

As for the reagent favoring the interaction between the $\alpha_2\delta$-1 subunit polypeptide and the radioligand as well as the Amersham SPA beads, the inventors found that imidazole could be efficiently used for that purpose when the $\alpha_2\delta$-1 subunit polypeptide is tagged with an amino acid sequence including 6 histidine residues. Furthermore, and more importantly, it was found that imidazole also enhanced binding of the radioligand to the $\alpha_2\delta$-1 polypeptide.

The optimal concentration of imidazole used to enhance radioligand binding varies depending on the concentration of $\alpha_2\delta$-1 subunit polypeptide used in the assay. For instance, when the concentration of the $\alpha_2\delta$-1 subunit polypeptide is about 20 µl ($\alpha_2\delta$-1 polypeptide concentration of 0.6 pmol/ul), imidazole concentrations ranging from 10 to 50 mM can be used, with concentrations ranging between 10 and 30 mM being preferred. A most preferred imidazole concentration is 20 mM. It is to be noted that other compounds such as histidine can be used to enhance radioligand binding. Furthermore, pH variations can also influence radioligand binding although pH variations should be closely monitored as they may have an effect on the structural configuration of the of $\alpha_2\delta$-1 subunit polypeptide. Also the use of imidazole is preferred to enhance radioligand binding, the person skilled in the art know that the use of imidazole is preferred but is absolutely not essential.

The concentration of the radioligand is evaluated with respect to the concentration of $\alpha_2\delta$-1 subunit polypeptide present in the assay medium. Generally, the concentration of radioligand varies from 1 nM to 100 nM. A preferred [^{3}H]gabapentin concentration is about 5 to 20 nM, with a most preferred concentration being about 10 nM. A preferred [^{3}H]leucine concentration is also about 5 to 20 nM, with a most preferred concentration being about 10 nM. It is to be noted that the concentration of other radioligands having affinities similar to those of [^{3}H]gabapentin and [^{3}H]leucine should also be in the range of about 5 to 20 nM.

Once the optimal radioligand binding conditions have been determined, a test ligand can be introduced in the assay medium to evaluate the level of displacement of the radioligand. The concentration of test ligand to be introduced in the assay medium usually varies from 0.1 nM to about 100 µM. A preferred test ligand concentration of about 10 µM is usually a starting point in a high throughput screening assay. Then, depending on the number of hits obtained, it may be lowered or increased.

It is to be noted that the parameters set forth above, which have been evaluated for a typical SPA assay using Amersham SPA beads can be adjusted by the skilled person, for example if SPA beads of a different type are used.

2) Flashplate assay

Similarly to the SPA assays, the flashplate can first be developed in order to optimize the conditions under which the radioligand binds the $\alpha_2\delta$-1 subunit polypeptide. The parameters which can be varied to optimize radioligand binding in a typical flashplate assay using NEN Ni chelate flashplates also include assay temperature, $\alpha_2\delta$-1 subunit polypeptide interaction with both the radioligand and the flashplates, radioligand concentration as well as pH variations.

The temperature at which the assay can be carried out can vary from 1 to 30°C. Preferred temperatures range from 18 to 23°C, with 21°C being the most preferred temperature.

The interaction of the $\alpha_2\delta$-1 subunit polypeptide with the flashplates can be optimized by adjusting the concentration of the polypeptide and by introducing a reagent which will favor this interaction. When a standard NEN Ni chelate flashplate is used, the $\alpha_2\delta$-1 subunit polypeptide volume usually varies between 0.5 and 20 µl for a concentration of $\alpha_2\delta$-1 subunit polypeptide of 0.6 pmol/ul. As the published maximum binding capacity of NEN plates is about 6 pmol per well, the inventors consider that an optimal concentration of $\alpha_2\delta$-1 subunit polypeptide is probably around 5 pmol per well at 8µl.

Also the use of imidazole is preferred to enhance radioligand binding, the person skilled in the art know that the use of imidazole is preferred but is absolutely not essential.

With regard to the reagent favoring the interaction between the $\alpha_2\delta$-1 subunit polypeptide and the radioligand as well as the flashplates, the inventors found that imidazole could also be efficiently used for that purpose when the $\alpha_2\delta$-1 subunit polypeptide is tagged with an amino acid sequence including 6 histidine residues. It was also found that imidazole concentrations substantially enhanced binding of the radioligand to the $\alpha_2\delta$-1 polypeptide. The optimal concentration of imidazole used to enhance radioligand binding varies

depending on the concentration of $\alpha_2\delta$-1 subunit polypeptide used in the assay. For instance, when the volume of the $\alpha_2\delta$-1 subunit polypeptide is about 10 µl µl ($\alpha_2\delta$-1 polypeptide concentration of 0.6 pmol/ul), the optimal imidazole concentration can vary between 1 and 20 mM, with a concentration of about 10 mM being preferred. As mentioned previously, other compounds such as histidine as well as pH variations may be used to enhance radioligand binding.

The concentration of the radioligand is evaluated with respect to the concentration of $\alpha_2\delta$-1 subunit polypeptide present in the assay medium. Generally, the concentration of radioligand varies from 1 nM to 100 nM. A preferred [^{3}H]gabapentin concentration is about 5 to 20 nM, with a most preferred concentration being about 10 nM. A preferred [^{3}H]leucine concentration is also about 5 to 20 nM, with a most preferred concentration being about 10 nM. It is to be noted that the concentration of other radioligands having affinities similar to those of [^{3}H]gabapentin and [^{3}H]leucine should also be in the range of about 5 to 20 nM.

Once the optimal radioligand binding conditions have been determined, a test ligand can be introduced in the assay medium to evaluate the level of displacement of the radioligand. The concentration of test ligand to be introduced in the assay medium usually varies from 0.1 nM to about 100 µM. A preferred test ligand concentration of about 10 µM is usually a starting point in a high throughput screening assay. Then, depending on the number of hits obtained, it may be lowered or increased.

The inventors have tested the displacement of a particular radioligand, [^{3}H]gabapentin, with (S+)-3-isobutyl gaba, (R-)-3-isobutyl gaba and gabapentin. The data provided in the examples which follow clearly shows that the assay can be used in high throughput competition studies.

Example 1

Construction of a nucleotide sequence encoding the putative soluble porcine $\alpha_2\delta$-1b deletion mutant of SEQ ID NO:9

a) Primer design

PCR primers were designed to generate the soluble porcine $\alpha_2\delta$-1b deletion mutant of SEQ ID NO:9 as follows:

5' PCR primer: This was designed to engineer in a KOZAK translation initiation consensus sequence prior to the coding sequence (Kozak *JBC* **266** 19867-19870)

3' PCR primer: This was designed to engineer in six histidine residues followed by a stop-codon at the desired location in the coding sequence. In addition to the stop codon the $\alpha_2\delta$-1 primers also included an *Eco* RI restriction site.

The bold region in each primer sequence denotes the 'tagged' region; addition of sequences not present in the template. Primers were custom synthesized by Perkin Elmer Applied Biosystems UK to the ABI ready pure grade, supplied lyophilized then resuspended to 15 μM in 10mM TE. JB189 and 195 were provided without 5' phosphate groups:

5' primer JB189 (5'-TCGCCACCATGGCTGCTGGCTGCCTGCTG-3', SEQ ID NO:20)

3' primer JB195 (5'-TCGGAATTCCTCAGTGATGGTGATGGTGATGAGAAACACCACCACAGTCGGT-3' ,SEQ ID NO:21)

b) PCR protocols for the generation of the $\alpha_2\delta$–1 deletion mutant

1) Generation of the pcDNA3-porcine-$\alpha_2\delta$–(+) PCR template

An oligo dT-primed λgt10 porcine cerebral cortical cDNA library was screened by ECL (Amersham) using a 2,381-bp *HindIII fragment* (coding sequence 268-2649) of the rabbit skeletal muscle $\alpha_2\delta$ clone (pcDNA3-Rab-$\alpha_2\delta$-(+) (supplied by Neurex) as the probe.

A positive insert was identified and subcloned into pBluescript-SK-(+) to generate pB-PC-$\alpha_2\delta$-1.1. The clone was sequenced on both strands, except for a 711-bp stretch at one end of the clone, which had a high degree of homology to mitochondrial C oxidase.

The $\alpha_2\delta$ coding region was homologous to the 3' region of the human neuronal $\alpha_2\delta$ sequence but lacked 926 bp of 5' coding sequence. The missing sequence was obtained by 5'-RACE using total RNA prepared from porcine cerebral cortex. RACE was performed across a *Bgl* I site unique in known $\alpha_2\delta$ sequences (rabbit (accession no. M21948)), rat (accession number M86621), human (accession no. M76559)

The sequence derived from the 5' RACE product was used to design a primer (JB042, 5'-GGGGATTGATCTTCGATCGCG-3'; SEQ ID NO:18) specific for the 5'-untranslated end of the cDNA. PCR was then performed with *Pfu* DNA polymerase using JB042 and a primer downstream of the *Bgl* I site (JB040, CTGAGATTTGGGGTTCTTTGG, SEQ ID NO:19).

The PCR product was ligated to Eco Rl linkers (5'-GGAATTCC-3') and then digested with Eco RI and *Bgl* I. The 1,564-bp fragment (5' portion of the $\alpha_2\delta$ cDNA) was gel-purified.

Similarly, a 2,303-bp fragment (3' portion of the $\alpha_2\delta$ cDNA) was isolated after digestion of pB-PC-$\alpha_2\delta$-1.1 with *Bgl* I and Eco Rl. The two fragments of $\alpha_2\delta$ cDNA were then ligated to EcoRI-digested pcDNA3 in a three-way ligation. A clone was picked with the full-length $\alpha_2\delta$ sequence in the positive orientation with respect to the cytomegalovirus promoter (pcDNA3-PC-$\alpha_2\delta$-(+)).

2) PCR protocol

The following reagents were added to obtain two cocktails labelled 'lower' and 'upper' buffers.

Lower	*µl*
10x *Pfu* DNA polymerase buffer	25
10mM dNTP's	5
100ng/µl pcDNA3-porcine-$\alpha_2\delta$-(+)	10
15µM JB189	8.5
15µM JB195	8.5
H_2O	193

Upper	*µl*
10x *Pfu* DNA polymerase buffer	25
H_2O	220
2.5units/µl *Pfu* DNA polymerase	5

50µl aliquots of lower buffer were added to each of four 0.5ml eppendorf tubes. To each was added one PCRgem 100 ampliwax bead (PE biosystems). Tubes were heated to 80°C for 2 minutes then cooled to 4°C. 50µl of upper buffer was then added to each tube. Tubes were then cycled on a Stratagene Robo-Cycler according to the following conditions: 98°C / 1min 30sec, followed by: for 20 cycles 98°C / 45sec, 54°C / 2min, 72°C / 6min, followed by: 72°C / 20min, followed by: hold at 4°C.

The 3228bp PCR product was then purified on a QIAquick PCR purification column (Qiagen) and eluted with 61µl of H_2O. The following reagents were added to the eluted DNA: 0.7µl 10mM ATP, 7µl 10x Polynucleotide Kinase buffer, 1µl 1unit/µl Polynucleotide Kinase.

The above 5' phosphorylation reaction was incubated at 37°C for 1 hour. The reaction was stopped by incubation at 65°C for 10min. The 3228bp 5' phosphorylated PCR product was then gel purified from a 1% agarose gel using QIAEX (Qiagen) beads and eluted in ~50µl.

Example 2

Cloning of the PCR fragments of Example 1 into the Baculovirus transfer vector pFastBac1

The PCR products of Example 1 (3228bp JB189/JB195 derived PCR product coding for 6His tagged porcine $\alpha_2\delta$-1b: SEQ ID No 9) were cloned into *Stu* I digested, calf intestinal phosphatase dephosphorylated, phenol chloroform extracted and QIAEX gel purified pFastBac1 (Life Technologies) using the Rapid DNA ligation kit (Roche Diagnostics) transforming XL1-blue ($\alpha_2\delta$-1b) *E. Coli* cells:

a) Screening for positive recombinants

Given that the PCR product was cloned by blunt-end ligation a screen was required to select a recombinant with the gene ligated in the positive orientation with respect to the polyhedrin promoter in pFastBac1. This was achieved by restriction digest of miniprep DNA (Qiagen miniprep kit) prepared from colony minicultures and analysis on a 1% TAE agarose gel. A positive clone was identified according to the following digest patterns:

SEQ ID No 9 in pFastBac1

Eco RI digest performed on miniprep DNA

	Predicted fragments (bp)
PCR product cloned in a positive orientation	4773 and 3230
PCR product cloned in a negative orientation	7989 and 14

b) Sequencing analysis of selected clones

One positive was selected for this clone and used to prepare a plasmid DNA stock of the desired construct (QIAGEN maxi kit). Confirmatory sequence reactions were performed using the Big Dye terminator sequencing kit and run on an ABI 310 Prism Genetic Analyzer. Sequence analysis of both coding strands was performed using a selection of sequencing oligonucleotide primers and has yielded the following results:

Sequencing of pFBac-Porcine-s-$\alpha_2\delta$-1-Δ1040-1067-6His confirmed that the insert sequence corresponded to the nucleic acid encoding the polypeptide of SEQ ID No 9, except for the deletion of two bases from the 5' end of the 5' PCR primer (JB189). The loss of these two bases did not have any impact on the 5' end of the gene as the KOZAK translation start-site consensus sequence (GCCACC) starts immediately after this deletion.

Example 3

Protocol for establishing baculovirus banks for the expression of the $\alpha_2\delta$–1 deletion mutant of SEQ ID NO:9

Essentially, the protocol used to generate the baculovirus banks is that outlined in the Life Technologies Bac-to Bac™ baculovirus expression systems manual.

a) Transposition f DH10Bac *E Coli* cells

One ng (5µl) of the recombinant pFastBac-1 construct containing the nucleotide sequence encoding the porcine $\alpha_2\delta$-1 deletion mutant of SEQ ID No 9 was added to 100µl of DH10Bac cells thawed on ice. The cells were then mixed gently by tapping the tube then incubated on ice for 30minutes before heat shock treatment by incubation in a 42°C water bath for 45 seconds. The mixture was then chilled on ice for 2 minutes before the addition of 900µl of S.O.C. medium. The mixture was then placed in a shaking incubator (200rpm) at 37°C for 4hours. The cells were then serially diluted (10 fold dilutions from 10^{-1} to 10^{-3}) and 10µl of each dilution plated on LB agar plates containing 50µg/ml kanamycin, 7µg/ml gentamicin, 10µg/ml tetracycline, 100µg/ml Bluo-gal and 40µg/ml IPTG. The plates were incubated at 37°C for between 1 and 3 days until discrete colonies of blue and white colour were discernible.

b) Isolation of recombinant DNA

White colonies (containing the recombinant bacmid) were picked and grown for 24 hours (to stationary phase) at 37°C with shaking (200rpm) in 2ml of LB containing 50µg/ml kanamycin, 7µg/ml gentamicin and 10µg/ml tetracycline. 1.5ml of culture was then transferred to a microfuge tube and centrifuged at 14,000xg for 1minute. The supernatant was removed and the cells resuspended gently in 0.3ml of 15mM Tris-HCl (pH8.0), 10mM EDTA, 100µg/ml RNase A. 0.3ml of 0.2N NaOH, 1% SDS was then added and the mixture mixed gently before incubation at 22°C for 5 minutes. Then 0.3ml of 3M potassium acetate (pH5.5) was added and the sample placed on ice for 10 minutes. After centrifugation at 14,000xg for 10 minutes the supernatant was transferred to a tube containing 0.8ml of isopropanol, mixed then placed on ice for 10 minutes before centrifugation at 14,000xg for 10 minutes. The supernatant was then discarded and the pellet rinsed with 0.5ml of 70% ethanol before centrifugation at 14,000xg for 5 minutes. This 70% ethanol rinse was then repeated before removing all of the supernatant and air drying the pellet for 10 minutes at room temperature. The pellet was finally resuspended in 40µl of TE.

c) Transfection of sf9 cells with the recombinant bacmid DNA

A 6-well tissue culture plate was seeded with $0.9x10^6$ sf9 cells (cells at log phase having grown from a culture passaged at $0.3x10^6$ cells/ml) per 35mm well in 2ml of Sf-900 II SFM media containing 50units/ml penicillin and 50µg/ml streptomycin. Cells were left to attach at 27°C for 1 hour. Bacmid DNA prepared as described above (5µl) was added to 200µl of Sf-900 II SFM media containing 6µl of CELLFECTIN and mixed before incubation at room temperature for 45 minutes. The cells were washed once with 2ml of Sf-900 II SFM media without antibiotics then 0.8ml of Sf-900 II SFM media was added to each tube containing the lipid-DNA complex. The wash buffer was removed from the cells and the 1ml of diluted lipid-DNA complex overlaid on the cells. The cells were incubated for 5hours at 27°C after which time the transfection mixture was removed and 2ml of Sf-900 II SFM media containing 50units/ml penicillin and 50µg/ml streptomycin was added. The cells were then incubated for 72 hours.

After incubation for 72 hours the media was removed from the cells and centrifuged at 500xg for 5 minutes. The supernatant was then transferred to a fresh tube, this was labelled as the P0 bank and stored at 4°C in the dark. The P1 bank was prepared by passaging sf9 cells at approx $5x10^6$ cells/ml to $2x10^6$ cells/ml (100ml in a 250ml Erlenmeyer flask) and adding 0.5ml of the P0 bank harvested above. The cells were then incubated shaking (200rpm) at 27°C for 4 days. Under sterile conditions the culture was centrifuged at 500xg for 10 minutes and the supernatant 0.2µM filtered (P1 bank). The P2 bank was prepared by adding 2ml of P1 bank per 400ml culture (in 1L Erlenmeyer flasks) passaged as above to $2x10^6$cells/ml. The culture was incubated as before for 4 days and the supernatant harvested and filtered as described for the P1 bank. The supernatant was first pooled then aliquoted (10ml) and stored at 4°C.

Example 4

Protein expression

To sf9 cells passaged from ~$5x10^6$ cells/ml to $2x10^6$ cells/ml in Sf-900 II SFM media was added 0.1ml virus per 100 ml of cells of the appropriate viral bank (400ml volumes in 1L Erlenmeyer flasks). The cells were then cultured for 4-5 days at 27°C with 110 rpm

shaking. Expression of the protein was confirmed by SDS-PAGE and Western blotting using an anti penta-His monoclonal antibody (Qiagen) and was detected in the culture supernatant and cell lysate.

Example 5

Purification of $\alpha_2\delta$-1deletion mutant of SEQ ID NO:9

The $\alpha_2\delta$-1 deletion mutant of SEQ ID NO:9 was purified from the cell lysate following the purification strategy outlined below:

The culture was centrifuged at 6,000xg for 10 minutes and the supernatant removed. The weight of the cell pellet was determined before re-suspension in 20mM Tris pH8.0, 100mMKCl, 1% P40-Nonidet (100ml per 20g of wet cells). A protease inhibitor cocktail (Sigma Cat# P8849), 1ml/L, was added to the mixture. The solution was then stirred for 10 minutes before centrifugation for 1hour at 30,000xg and 4°C. The supernatant was concentrated (30kDa cut off) to approx. ~300ml then centrifuged for 1hour at 100,000xg.

Supernatant containing the soluble proteins was diluted 1:3 in 10mM Tris-HCl pH8.0 (equilibration buffer) and loaded onto a pre-equilibrated Q-Sepharose column (2.5cm i.d. x 30cm h.) at a flow rate of 900ml/h. After washing with equilibration buffer until a stable A_{280nm} baseline had been achieved, protein was eluted with 20mM Tris-HCl pH8.0, 0.5M KCl, 10mM Imidazole.

The eluate was then loaded onto a Ni-NTA (Qiagen) column (2.5cm i.d. x 6cm h.) pre-equilibrated in 20mM Tris pH8.0, 0.5M KCl, 10mM Imidazole at a flow rate of 2 ml/min. The column was washed successively with buffer A (20mM Tris pH8.0, 0.5M KCl, 20mM Imidazole), buffer B (100mM Tris-HCl pH8.0, 1M KCl), and buffer A again. Elution was performed with buffer C (20mM Tris-HCl pH8.0, 100mM KCl, 0.5M Imidazole). The Ni-NTA eluate (~50ml) was concentrated (30kDa cut-off) to ~2ml and applied at 1ml/min and in 0.2ml aliquots, to an FPLC Superdex-200 column equilibrated in 10mM HEPES, pH7.4, 150mM NaCl. Fractions containing the polypeptide of SEQ ID No 9 were pooled. As shown in Figure 1, the protein elution profile and associated [^{3}H]gabapentin binding activity is presented together with a silver-stained SDS-PAGE gel (post Ni NTA load of

Superdex-200) demonstrating the co-elution of the ~130kDa band ($\alpha_2\delta$) with the [^{3}H]gabapentin binding activity and A_{280nm} profile.

Example 6

SPA assay of [^{3}H]gabapentin binding to soluble porcine $\alpha_2\delta$-1b-6His

The assay was carried out at 21°C. Assay components were added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C) to 96-well Optiplates:

25µl imidazole at various concentrations (diluted from a 1M stock pH8.0, see assay details)

50µl 10mM HEPES pH 7.4

25µl (50mg) SPA beads (Amersham)

100µl s-$\alpha_2\delta$-1b-6His of SEQ ID No 9 (2µl protein diluted to 100µl) obtained from example 5

25µl radioligand ([^{3}H]gabapentin)

Immediately after adding radioligand, the optiplates were loaded in the Packard Top Count scintillation counter to follow the binding time course. Imidazole was first used in the assay to optimize the specific interaction of the protein's 6His tag with the SPA bead. Imidazole itself (up to 100mM) in the filtration assay has no effect on [^{3}H]gabapentin binding (n=1).

As shown in figure 2, specific binding of [^{3}H]gabapentin to the s-$\alpha_2\delta$-1b-6His was enhanced by imidazole. Of the concentrations, tested the optimal was 50mM. Equilibration was reached after ~2hours.

Example 7

Ni Flashplate assay of [^{3}H]gabapentin binding to soluble porcine $\alpha_2\delta$-1b-6His (SEQ ID No 9)

Assays were carried out at 21°C in a final volume of 250µl in 96-well NEN Ni chelate flash plates. Assay components were added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl 10mM HEPES pH7.4

25µl imidazole at various concentrations (diluted from a 1M stock pH8.0, see assay details)
75µl 10mM HEPES pH 7.4
100µl s-$\alpha_2\delta$-1b-6His (2µl protein diluted to 100µl) obtained from example 5
25µl radioligand ([^{3}H]gabapentin)

Immediately after adding the radioligand, flash plates were loaded in the Packard Top Count scintillation counter to follow the binding time course. The '[^{3}H] flash plate' programme (cpm) was used to monitor activity. Imidazole was first used in the assay to optimize the specific interaction of the protein's 6His tag with the Ni flashplate. Imidazole itself (up to 100mM) in the filtration assay has no effect on [^{3}H]gabapentin binding (n=1).

As shown in figure 3, the specific binding of [^{3}H]gabapentin to the s-$\alpha_2\delta$-1b-6His was enhanced by imidazole. Initially, from the concentrations tested, the best concentration was found to be 10mM.
Specific binding was determined at different volumes of s-$\alpha_2\delta$-1b-6His, in the presence of 10mM imidazole, over a time period of 10h. Results are shown in figure 4 and equilibrium was reached at ~3h. Specific binding increased linearly with increasing amounts of protein, up to 8µl, after which the binding capacity of the Ni chelate in the assay well was probably exceeded (see figure 5). The published maximum binding capacity of NEN plates is 6pmol/well. The concentration of purified s-$\alpha_2\delta$-1b-6His is estimated at ~0.6pmol/µl, which yields 5pmol/well at 8µl.

Table 2
Saturation studies

Saturation experiments were performed with 12 duplicate data points, [^{3}H]gabapentin concentration ranged from ~1 to 350nM. Data was analyzed using KEL-RADLIG for Windows.

Flash plate (2µl protein used, n=2)	**Filter binding** K_D(nm) (4µl protein used, n=3)
K_D, 9.32nM K_D, 10.5nM **Mean = 9.91nM**	K_D, 12.3nM K_D, 8.91nM K_D, 10.6nM **Mean = 10.60 ± 0.98nM**

Example 8

Ni Flashplate assay of [^{3}H]Leucine binding to soluble porcine $\alpha_2\delta$-1b-6His

The procedure described in example 2 was repeated, except that [^{3}H]gabapentin was replaced by 25 µl (10.1 nM) of [^{3}H]Leucine, as shown in figure 8, [^{3}H]Leucine binds with high affinity to soluble $\alpha_2\delta$-1b-6His. This demonstrates that it is possible to use commercially available forms of [^{3}H]Leucine in replacement of [^{3}H]gabapentin in the assay.

Example 9

Ni Flashplate assay studying competitive binding of [^{3}H]gabapentin, (S+)-3-isobutyl GABA and (R-)-3-isobutyl GABA to porcine $\alpha_2\delta$-1b-6His (SEQ ID No 9)

Assays were carried out at 21°C in a final volume of 250µl in 96-well NEN Ni chelate flash plates. Wells were set up for both 'total' and 'non-specific' binding. Specific binding was defined as that remaining after subtraction of the average of the 'non-specific binding' values from the average of the 'total' binding values. Assay components were added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

	25µl	10mM HEPES pH7.4 or 25 µl of the test compound at the appropriate concentration in HEPES
	25µl	200 mM imidazole (diluted from a 1M stock pH8.0, see assay details)
Total binding	75µl	10mM HEPES pH 7.4
Non-specific binding	50µl	10mM HEPES pH 7.4 and 25µl 100µM (S+)-3-isobutyl GABA
	100µl	s-$\alpha_2\delta$-1b-6His (2µl protein* diluted to 100µl)
	25µl	radioligand ([^{3}H]gabapentin or [^{3}H]Leucine)

* The source of s-$\alpha_2\delta$-1b-6His was that purified by FPLC Superdex-200 gel filtration (see example 5)

Immediately after adding radioligand, flash plates were loaded in the Packard Top Count scintillation counter to follow the binding time course. Incubation time before the assay

was 3 hours. The '[^{3}H] flash plate' programme (cpm) was used to monitor activity. Specific binding was ~98% of the 'total' value. Imidazole was used in the assay to optimize the specific interaction of the protein's 6His tag with the Ni flashplate. Imidazole itself (up to 100mM) in the filtration assay has no effect on [^{3}H]gabapentin binding (n=1).

Competition studies were compared across the flash-plate and filter binding methodologies in order to validate the new assay technology with the established filter binding methodology.

GraphPad Prism software was used to process competition curve data and determine IC_{50} and hill slope values. Twelve point competition curves with half log dilution steps of test compounds were used in the experiments. Results are shown in Table 3 below where IC50 values are presented, and in figure 9 where hill slopes range from -0.9 to 1.3. The [^{3}H]Gabapentin concentration used in assay is in the range of 10-13nM

Table 3

Competition studies:

GraphPad Prism software was used to process competition curve data and determine IC_{50} and hill slope values. Ten point competition curves with half log dilution steps of test compounds were used in the experiments.

IC_{50} values were converted to Ki values (presented in table) according to the following equation:

$Ki = IC_{50} / (1+[L]/K_D)$

The K_D values used were those mean values presented in table 1.

The [^{3}H]Gabapentin concentration in the assay ranged from 10-13nM and was determined for each experiment for the purpose of calculating the Ki value as described above.

Hill slopes were all in the range of –0.9 to 1.3

Test compound	Flash plate (3µl protein used, n=2)	Filter binding K_D(nm) (4µl protein used, n=3)
Gabapentin	10.4 7.97	7.13 7.70 10.2
Mean (geometric)	*9.10nM*	*7.84nM*
(S+)-3-isobutyl GABA	10.9 7.58	6.52 6.21 8.29
Mean (geometric)	*9.09nM*	*6.95nM*
(R-)-3-isobtyl GABA	157 207	78.4 64.2 107
Mean (geometric)	*180nM*	*81.5nM*

Example 10

Filter binding assay of [^{3}H]gabapentin binding to the recombinant polypeptide of SEQ ID No 9

Assays were carried out at 21°C in a final volume of 250µl in 96-deep well plates. Assay components were (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

25µl compound to test

200µl Polypeptide of SEQ ID No 9 (3µl protein diluted to 200µl)

25µl radioligand ([^{3}H]gabapentin (65Ci/mmole)

Plates were incubated at room temperature for 1h prior to filtering on to 96-well GF/B Unifilter plates pre-soaked in 0.3% polyethylenimine. Filters were washed with 3x1ml 50mM Tris-HCl (pH 7.4 at 4°C), and dried over-night. Scintillant (Microscint O, 50µl) was added and the plates counted using a Packard Top Count scintillation counter. Specific binding was ~98% of the 'total' value. In [^{3}H]gabapentin saturation studies, the K_D (nM) obtained was about 10.62.

Utility Application

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SEQUENCE LISTING

1- porcine nucleotide sequenc alpha2 delta-1

GGGGATTGATCTTCGATCGCGAAGATGGCTGCTGGCTGCCTGCTGGCCTTGACTCTGACAC
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GCCCAGGATGTAAGCTGTTTTCAACACCTTGTCCAAGCAAATGTAAGAAATAAGAAAGTGC
TGAAAGATGCAGTTAATAATATCACAGCAAAAGGAATCACAGATTACAAGAAGGGCTTTAG
TTTTGCTTTTGAACAACTGCTTAATTATAACGTTTCTAGAGCCAACTGCAATAAGATTATC
ATGTTGTTCACCGATGGAGGAGAAGAGAGAGCTCAGGAGATATTTGCCAAATACAACAAAG
ACAAAAAAGTACGTGTATTCACATTTTCAGTTGGTCAACATAATTATGACAGAGGACCTAT
TCAGTGGATGGCCTGTGAAAATAAAGGTTATTATTATGAAATTCCTTCCATTGGAGCAATC
AGAATCAATACTCAGGAATATTTGGATGTTCTGGGAAGACCAATGGTTTTAGCAGGAGACA
AAGCTAAGCAAGTCCAGTGGACAAACGTGTACCTGGATGCACTGGAACTGGGACTTGTCAT
TACTGGAACTCTTCCGGTCTTCAACATAACCGGCCAAAATGAAAATAAGACGAACTTAAAG
AACCAGCTGATTCTTGGTGTGATGGGAGTTGATGTATCTTTGGAAGATATTAAAAGACTGA
CACCACGTTTTACACTGTGCCCCAATGGCTATTACTTTGCAATTGATCCTAATGGCTATGT
TTTATTACATCCAAATCTTCAGCCAAAGAACCCCAAATCTCAGGAGCCAGTAACCTTGGAT
TTCCTTGATGCAGAATTAGAGAATGATATTAAAGTGGAGATCCGAAATAAAATGATAGATG
GAGAAAGTGGAGAAAAAACATTCAGAACTCTGGTTAAATCTCAAGATGAGAGATATATTGA
CAAAGGAAACAGGACATATACATGGACTCCTGTCAATGGCACAGATTACAGTTTGGCCTTG

GTATTACCAACCTACAGTTTTTACTATATAAAAGCCAAAATAGAAGAGACAATAACTCAGG
CCAGATCAAAAAAGGGCAAAATGAAGGATTCAGAAACACTGAAGCCTGATAATTTTGAAGA
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AAACATATGAGGACAGCTTCTATAAAAGAAGTCTAGATAACGATAACTATGTTTTCACTGC
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CTTTTGATGGCAAATCATGATGATTATACTAACCAGATTGGAAGGTTTTTTGGAGAGATTG
ACCCAAGTTTGATGAGACACCTGGTTAATATATCAGTTTATGCTTTTAACAAATCTTACGA
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CTATTCTACAGCAGTTTCTCTTGAGTTTGACCTTTCCACGACTTCTTGAAGCAGTTGAGAT
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ACAATGCCTTGGAGGATTATACCGACTGTGGTGGTGTTTCTGGATTAAATCCCTCCCTGTG
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TTATGACCCTTCTAAAACCAAATCTGCATATTAAACTTCAGACCCTGCCAGAATAGGAGCC
CTCAATTGCATTAAAATAGGGTAAACTGCAGAATCAGCAGAACTCTAGCTGGGCCCATCCC
ATGGCATCAATCTCAGACTCATAAGGCACCCACTGGCTGCATGTCAGGGTGTCAGATCCTG
AAACTTGTGTGAATGCTGCATCATCTATGTATAACATCAGAGCAAAATTCTATACCTATTC
TATTGGAAAATTTGAGAATTTGTTGTTGCATTGTTGGTGATTACATGTAAAAGGGCTCCCC
ACACAGTTGTGTATGAATCACGCAAATTGTCTTGATTTTGACTTGCTGCAATCCTTGTCCT
TTTACCAAGAAAATCTCTAGAGGGAAAAAAAAAGTCTTTTTTTTCCTTCACTAATTCTGCT

ACAAATTATTTCCTGCTTGGAGTAGTTATTATTAAAAAATATATATATAGAGAGAGAGAGA
GAGAATTAACATTGGTGTAATCTGTCAAAATAGAAATAATGGCTTATTTTCTACAAAAAA

2 - porcine nucleotide sequence

ATGGCTGCTGGCTGCCTGCTGGCCTTGACTCTGACACTTTTCCAATCTTTGCTGATCGGTC
CCTCATCGCAGGAGCCGTTCCCGTCGGCCGTCACTATCAAGTCATGGGTGGATAAAATGCA
AGAAGACCTTGTCACCCTGGCAAAAACAGCAAGTGGAGTCAATCAGCTTGTCGATATTTAT
GAAAAATACCAAGATTTGTATACTGTGGAACCAAATAATGCACGCCAGCTGGTGGAAATTG
CAGCCAGGGATATTGAGAAACTTCTGAGCAACAGATCTAAAGCCCTGGTGCGCCTAGCTTT
GGAAGCAGAGAAGGTTCAAGCAGCCCACCAGTGGAGAGAGGATTTTGCAAGCAATGAAGTT
GTCTACTACAATGCAAAGGATGATCTCGATCCTGAAAAAAATGACAGTGAGCCAGGCAGCC
AGAGGATAAAACCTGTTTTTATTGATGATGCTAATTTTGGGCGACAGATATCTTATCAGCA
TGCAGCAGTCCATATTCCCACCGACATCTATGAGGGCTCAACAATTGTGTTAAATGAACTG
AACTGGACAAGTGCCTTAGATGAAGTTTTCAAGAAAAATCGAGAGGAAGATCCCTCATTAT
TGTGGCAGGTGTTTGGCAGTGCCACAGGCCTGGCCCGGTATTATCCAGCTTCTCCATGGGT
TGATAACAGTAGAACTCCAAACAAGATTGACCTTTATGATGTACGAAGGAGACCATGGTAC
ATCCAAGGAGCTGCATCTCCTAAAGATATGCTTATTCTGGTCGACGTGAGTGGAAGTGTTA
GTGGTTTGACGCTTAAACTGATCCGAACATCTGTCTCTGAAATGTTGGAAACCCTCTCAGA
TGACGATTTTGTGAATGTAGCTTCATTTAACAGCAATGCCCAGGATGTAAGCTGTTTTCAA
CACCTTGTCCAAGCAAATGTAAGAAATAAGAAAGTGCTGAAAGATGCAGTTAATAATATCA
CAGCAAAAGGAATCACAGATTACAAGAAGGGCTTTAGTTTTGCTTTTGAACAACTGCTTAA
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GAGAGAGCTCAGGAGATATTTGCCAAATACAACAAAGACAAAAAAGTACGTGTATTCACAT
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CCAAAACATCAATCAGGGATCCGTGTGCTGGTCCAGTTTGTGATTGTAAAAGAAACAGTGA
TGTAATGGATTGTGTGATTCTAGATGATGGTGGGTTTCTTTTGATGGCAAATCATGATGAT
TATACTAACCAGATTGGAAGGTTTTTTGGAGAGATTGACCCAAGTTTGATGAGACACCTGG
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TGCTGCACCAAAACAAGGAGCAGGACATCGCTCAGCATATGTGCCATCAATAGCAGACATC
TTACACATTGGCTGGTGGGCCACTGCAGCTGCATGGTCTATTCTACAGCAGTTTCTCTTGA
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TCTGTCAAAGCAGAGTTGCATTACTGAACAAACCCAGTATTTCTTTGATAATGATAGCAAA
TCCTTCAGTGGGGTCTTGGACTGTGGTAACTGTTCCAGAATCTTTCACGTTGAAAAACTTA
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ATTGTGA

3 - porcine nucleotide sequence

ATGGCTGCTGGCTGCCTGCTGGCCTTGACTCTGACACTTTTCCAATCTTTGCTGATCGGTC
CCTCATCGCAGGAGCCGTTCCCGTCGGCCGTCACTATCAAGTCATGGGTGGATAAAATGCA
AGAAGACCTTGTCACCCTGGCAAAAACAGCAAGTGGAGTCAATCAGCTTGTCGATATTTAT
GAAAAATACCAAGATTTGTATACTGTGGAACCAAATAATGCACGCCAGCTGGTGGAAATTG
CAGCCAGGGATATTGAGAAACTTCTGAGCAACAGATCTAAAGCCCTGGTGCGCCTAGCTTT
GGAAGCAGAGAAGGTTCAAGCAGCCCACCAGTGGAGAGAGGATTTTGCAAGCAATGAAGTT
GTCTACTACAATGCAAAGGATGATCTCGATCCTGAAAAAAATGACAGTGAGCCAGGCAGCC

AGAGGATAAAACCTGTTTTTATTGATGATGCTAATTTTGGGCGACAGATATCTTATCAGCA
TGCAGCAGTCCATATTCCCACCGACATCTATGAGGGCTCAACAATTGTGTTAAATGAACTG
AACTGGACAAGTGCCTTAGATGAAGTTTTCAAGAAAAATCGAGAGGAAGATCCCTCATTAT
TGTGGCAGGTGTTTGGCAGTGCCACAGGCCTGGCCCGGTATTATCCAGCTTCTCCATGGGT
TGATAACAGTAGAACTCCAAACAAGATTGACCTTTATGATGTACGAAGGAGACCATGGTAC
ATCCAAGGAGCTGCATCTCCTAAAGATATGCTTATTCTGGTCGACGTGAGTGGAAGTGTTA
GTGGTTTGACGCTTAAACTGATCCGAACATCTGTCTCTGAAATGTTGGAAACCCTCTCAGA
TGACGATTTTGTGAATGTAGCTTCATTTAACAGCAATGCCCAGGATGTAAGCTGTTTTCAA
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ACGTGTACCTGGATGCACTGGAACTGGGACTTGTCATTACTGGAACTCTTCCGGTCTTCAA
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TATACTAACCAGATTGGAAGGTTTTTTGGAGAGATTGACCCAAGTTTGATGAGACACCTGG
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TGCTGCACCAAAACAAGGAGCAGGACATCGCTCAGCATATGTGCCATCAATAGCAGACATC
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GTTTGACCTTTCCACGACTTCTTGAAGCAGTTGAGATGGAAGATGATGACTTTACCGCCTC
TCTGTCAAAGCAGAGTTGCATTACTGAACAAACCCAGTATTTCTTTGATAATGATAGCAAA
TCCTTCAGTGGGGTCTTGGACTGTGGTAACTGTTCCAGAATCTTTCACGTTGAAAAACTTA
TGAACACCAACTTAATATTCATAATGGTTGAGAGCAAAGGGACTTGTCCTTGTGACACACG
ATTGCTCATACAAGCTGAGCAGACTTCTGACGGTCCAGATCCTTGTGATATGGTTAAGTGA

4 - porcine nucleotide sequence

ATGGCTGCTGGCTGCCTGCTGGCCTTGACTCTGACACTTTTCCAATCTTTGCTGATCGGTC
CCTCATCGCAGGAGCCGTTCCCGTCGGCCGTCACTATCAAGTCATGGGTGGATAAAATGCA
AGAAGACCTTGTCACCCTGGCAAAAACAGCAAGTGGAGTCAATCAGCTTGTCGATATTTAT
GAAAAATACCAAGATTTGTATACTGTGGAACCAAATAATGCACGCCAGCTGGTGGAAATTG
CAGCCAGGGATATTGAGAAACTTCTGAGCAACAGATCTAAAGCCCTGGTGCGCCTAGCTTT
GGAAGCAGAGAAGGTTCAAGCAGCCCACCAGTGGAGAGAGGATTTTGCAAGCAATGAAGTT
GTCTACTACAATGCAAAGGATGATCTCGATCCTGAAAAAAATGACAGTGAGCCAGGCAGCC
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TGCAGCAGTCCATATTCCCACCGACATCTATGAGGGCTCAACAATTGTGTTAAATGAACTG
AACTGGACAAGTGCCTTAGATGAAGTTTTCAAGAAAAATCGAGAGGAAGATCCCTCATTAT
TGTGGCAGGTGTTTGGCAGTGCCACAGGCCTGGCCCGGTATTATCCAGCTTCTCCATGGGT
TGATAACAGTAGAACTCCAAACAAGATTGACCTTTATGATGTACGAAGGAGACCATGGTAC
ATCCAAGGAGCTGCATCTCCTAAAGATATGCTTATTCTGGTCGACGTGAGTGGAAGTGTTA
GTGGTTTGACGCTTAAACTGATCCGAACATCTGTCTCTGAAATGTTGGAAACCCTCTCAGA
TGACGATTTTGTGAATGTAGCTTCATTTAACAGCAATGCCCAGGATGTAAGCTGTTTTCAA
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TCCTTCAGTGGGGTCTTGGACTGTGGTAACTGTTCCAGAATCTTTCACGTTGAAAAACTTA
TGAACACCAACTTAATATTCATAATGGTTGAGAGCAAAGGGACTTGTCCTTGTGACACACG

ATTGCTCATACAAGCTGAGCAGACTTCTGACGGTCCAGATCCTTGTGATATGGTTAAGCAA
CCCAGATACCGAAAAGGGCCTGATGTCTGTTTTGATAACAATGCCTTGGAGGATTATACCG
ACTGTGGTGGTGTTTCTTGA

5 - porcine amino acid sequence alpha2 delta-1

MAAGCLLALTLTLFQSLLIGPSSQEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVRLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIDDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL
NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE
ERAQEIFAKYNKDKKVRVFTFSVGQHNYDRGPIQWMACENKGYYYEIPSIGAIRINTQEYL
DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQNENKTNLKNQLILGVM
GVDVSLEDIKRLTPRFTLCPNGYYFAIDPNGYVLLHPNLQPKNPKSQEPVTLDFLDAELEN
DIKVEIRNKMIDGESGEKTFRTLVKSQDERYIDKGNRTYTWTPVNGTDYSLALVLPTYSFY
YIKAKIEETITQARSKKGKMKDSETLKPDNFEESGYTFIAPRDYCNDLKISDNNTEFLLNF
NEFIDRKTPNNPSCNTDLINRVLLDAGFTNELVQNYWSKQKNIKGVKARFVVTDGGITRVY
PKEAGENWQENPETYEDSFYKRSLDNDNYVFTAPYFNKSGPGAYESGIMVSKAVEIYIQGK
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YTNQIGRFFGEIDPSLMRHLVNISVYAFNKSYDYQSVCEPGAAPKQGAGHRSAYVPSIADI
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SFSGVLDCGNCSRIFHVEKLMNTNLIFIMVESKGTCPCDTRLLIQAEQTSDGPDPCDMVKQ
PRYRKGPDVCFDNNALEDYTDCGGVSGLNPSLWSIFGIQCVLLWLLSGSRHYQL

6 - porcine amino acid sequence

MAAGCLLALTLTLFQSLLIGPSSQEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVRLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIDDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL
NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE

ERAQEIFAKYNKDKKVRVFTFSVGQHNYDRGPIQWMACENKGYYYEIPSIGAIRINTQEYL
DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQNENKTNLKNQLILGVM
GVDVSLEDIKRLTPRFTLCPNGYYFAIDPNGYVLLHPNLQPKNPKSQEPVTLDFLDAELEN
DIKVEIRNKMIDGESGEKTFRTLVKSQDERYIDKGNRTYTWTPVNGTDYSLALVLPTYSFY
YIKAKIEETITQARSKKGKMKDSETLKPDNFEESGYTFIAPRDYCNDLKISDNNTEFLLNF
NEFIDRKTPNNPSCNTDLINRVLLDAGFTNELVQNYWSKQKNIKGVKARFVVTDGGITRVY
PKEAGENWQENPETYEDSFYKRSLDNDNYVFTAPYFNKSGPGAYESGIMVSKAVEIYIQGK
LLKPAVVGIKIDVNSWIENFTKTSIRDPCAGPVCDCKRNSDVMDCVILDDGGFLLMANHDD
YTNQIGRFFGEIDPSLMRHLVNISVYAFNKSYDYQSVCEPGAAPKQGAGHRSAYVPSIADI
LHIGWWATAAAWSILQQFLLSLTFPRLLEAVEMEDDDFTASLSKQSCITEQTQYFFDNDSK
SFSGVLDCGNCSRIFHVEKLMNTNLIFIMVESKGTCPCDTRL

7 - porcine amino acid sequence

MAAGCLLALTLTLFQSLLIGPSSQEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVRLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIDDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL
NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE
ERAQEIFAKYNKDKKVRVFTFSVGQHNYDRGPIQWMACENKGYYYEIPSIGAIRINTQEYL
DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQNENKTNLKNQLILGVM
GVDVSLEDIKRLTPRFTLCPNGYYFAIDPNGYVLLHPNLQPKNPKSQEPVTLDFLDAELEN
DIKVEIRNKMIDGESGEKTFRTLVKSQDERYIDKGNRTYTWTPVNGTDYSLALVLPTYSFY
YIKAKIEETITQARSKKGKMKDSETLKPDNFEESGYTFIAPRDYCNDLKISDNNTEFLLNF
NEFIDRKTPNNPSCNTDLINRVLLDAGFTNELVQNYWSKQKNIKGVKARFVVTDGGITRVY
PKEAGENWQENPETYEDSFYKRSLDNDNYVFTAPYFNKSGPGAYESGIMVSKAVEIYIQGK
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YTNQIGRFFGEIDPSLMRHLVNISVYAFNKSYDYQSVCEPGAAPKQGAGHRSAYVPSIADI
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8 - porcin amino acid sequence

MAAGCLLALTLTLFQSLLIGPSSQEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVRLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIDDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL
NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE
ERAQEIFAKYNKDKKVRVFTFSVGQHNYDRGPIQWMACENKGYYYEIPSIGAIRINTQEYL
DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQNENKTNLKNQLILGVM
GVDVSLEDIKRLTPRFTLCPNGYYFAIDPNGYVLLHPNLQPKNPKSQEPVTLDFLDAELEN
DIKVEIRNKMIDGESGEKTFRTLVKSQDERYIDKGNRTYTWTPVNGTDYSLALVLPTYSFY
YIKAKIEETITQARSKKGKMKDSETLKPDNFEESGYTFIAPRDYCNDLKISDNNTEFLLNF
NEFIDRKTPNNPSCNTDLINRVLLDAGFTNELVQNYWSKQKNIKGVKARFVVTDGGITRVY
PKEAGENWQENPETYEDSFYKRSLDNDNYVFTAPYFNKSGPGAYESGIMVSKAVEIYIQGK
LLKPAVVGIKIDVNSWIENFTKTSIRDPCAGPVCDCKRNSDVMDCVILDDGGFLLMANHDD
YTNQIGRFFGEIDPSLMRHLVNISVYAFNKSYDYQSVCEPGAAPKQGAGHRSAYVPSIADI
LHIGWWATAAAWSILQQFLLSLTFPRLLEAVEMEDDDFTASLSKQSCITEQTQYFFDNDSK
SFSGVLDCGNCSRIFHVEKLMNTNLIFIMVESKGTCPCDTRLLIQAEQTSDGPDPCDMVKQ
PRYRKGPDVCFDNNALEDYTDCGGVS

9 - porcine amino acid sequence

MAAGCLLALTLTLFQSLLIGPSSQEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVRLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIDDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL
NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE
ERAQEIFAKYNKDKKVRVFTFSVGQHNYDRGPIQWMACENKGYYYEIPSIGAIRINTQEYL
DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQNENKTNLKNQLILGVM
GVDVSLEDIKRLTPRFTLCPNGYYFAIDPNGYVLLHPNLQPKNPKSQEPVTLDFLDAELEN
DIKVEIRNKMIDGESGEKTFRTLVKSQDERYIDKGNRTYTWTPVNGTDYSLALVLPTYSFY
YIKAKIEETITQARSKKGKMKDSETLKPDNFEESGYTFIAPRDYCNDLKISDNNTEFLLNF

NEFIDRKTPNNPSCNTDLINRVLLDAGFTNELVQNYWSKQKNIKGVKARFVVTDGGITRVY
PKEAGENWQENPETYEDSFYKRSLDNDNYVFTAPYFNKSGPGAYESGIMVSKAVEIYIQGK
LLKPAVVGIKIDVNSWIENFTKTSIRDPCAGPVCDCKRNSDVMDCVILDDGGFLLMANHDD
YTNQIGRFFGEIDPSLMRHLVNISVYAFNKSYDYQSVCEPGAAPKQGAGHRSAYVPSIADI
LHIGWWATAAAWSILQQFLLSLTFPRLLEAVEMEDDDFTASLSKQSCITEQTQYFFDNDSK
SFSGVLDCGNCSRIFHVEKLMNTNLIFIMVESKGTCPCDTRLLIQAEQTSDGPDPCDMVKQ
PRYRKGPDVCFDNNALEDYTDCGGVSHHHHHH

10 - human nucleotide sequence

ATGGCTGCTGGCTGCCTGCTGGCCTTGACTCTGACACTTTTCCAATCTTTGCTCATCGGCC
CCTCGTCGGAGGAGCCGTTCCCTTCGGCCGTCACTATCAAATCATGGGTGGATAAGATGCA
AGAAGACCTTGTCACACTGGCAAAAACAGCAAGTGGAGTCAATCAGCTTGTTGATATTTAT
GAGAAATATCAAGATTTGTATACTGTGGAACCAAATAATGCACGCCAGCTGGTAGAAATTG
CAGCCAGGGATATTGAGAAACTTCTGAGCAACAGATCTAAAGCCCTGGTGAGCCTGGCATT
GGAAGCGGAGAAAGTTCAAGCAGCTCACCAGTGGAGAGAAGATTTTGCAAGCAATGAAGTT
GTCTACTACAATGCAAAGGATGATCTCGATCCTGAGAAAAATGACAGTGAGCCAGGCAGCC
AGAGGATAAAACCTGTTTTCATTGAAGATGCTAATTTTGGACGACAAATATCTTATCAGCA
CGCAGCAGTCCATATTCCTACTGACATCTATGAGGGCTCAACAATTGTGTTAAATGAACTC
AACTGGACAAGTGCCTTAGATGAAGTTTTCAAAAAGAATCGCGAGGAAGACCCTTCATTAT
TGTGGCAGGTTTTTGGCAGTGCCACTGGCCTAGCTCGATATTATCCAGCTTCACCATGGGT
TGATAATAGTAGAACTCCAAATAAGATTGACCTTTATGATGTACGCAGAAGACCATGGTAC
ATCCAAGGAGCTGCATCTCCTAAAGACATGCTTATTCTGGTGGATGTGAGTGGAAGTGTTA
GTGGATTGACACTTAAACTGATCCGAACATCTGTCTCCGAAATGTTAGAAACCCTCTCAGA
TGATGATTTCGTGAATGTAGCTTCATTTAACAGCAATGCTCAGGATGTAAGCTGTTTTCAG
CACCTTGTCCAAGCAAATGTAAGAAATAAAAAAGTGTTGAAAGACGCGGTGAATAATATCA
CAGCCAAAGGAATTACAGATTATAAGAAGGGCTTTAGTTTTGCTTTTGAACAGCTGCTTAA
TTATAATGTTTCCAGAGCAAACTGCAATAAGATTATTATGCTATTCACGGATGGAGGAGAA
GAGAGAGCCCAGGAGATATTTAACAAATACAATAAAGATAAAAAAGTACGTGTATTCAGGT
TTTCAGTTGGTCAACACAATTATGAGAGAGGACCTATTCAGTGGATGGCCTGTGAAAACAA
AGGTTATTATTATGAAATTCCTTCCATTGGTGCAATAAGAATCAATACTCAGGAATATTTG
GATGTTTTGGGAAGACCAATGGTTTTAGCAGGAGACAAAGCTAAGCAAGTCCAATGGACAA
ATGTGTACCTGGATGCATTGGAACTGGGACTTGTCATTACTGGAACTCTTCCGGTCTTCAA

CATAACCGGCCAATTTGAAAATAAGACAAACTTAAAGAACCAGCTGATTCTTGGTGTGATG
GGAGTAGATGTGTCTTTGGAAGATATTAAAAGACTGACACCACGTTTTACACTGTGCCCCA
ATGGGTATTACTTTGCAATCGATCCTAATGGTTATGTTTTATTACATCCAAATCTTCAGCC
AAAGAACCCCAAATCTCAGGAGCCAGTAACATTGGATTTCCTTGATGCAGAGTTAGAGAAT
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GACACCTGTCAATGGCACAGATTACAGTTTGGCCTTGGTATTACCAACCTACAGTTTTTAC
TATATAAAAGCCAAACTAGAAGAGACAATAACTCAGGCCAGATCAAAAAAGGGCAAAATGA
AGGATTCGGAAACCCTGAAGCCAGATAATTTTGAAGAATCTGGCTATACATTCATAGCACC
AAGAGATTACTGCAATGACCTGAAAATATCGGATAATAACACTGAATTTCTTTTAAATTTC
AACGAGTTTATTGATAGAAAAACTCCAAACAACCCATCATGTAACGCGGATTTGATTAATA
GAGTCTTGCTTGATGCAGGCTTTACAAATGAACTTGTCCAAAATTACTGGAGTAAGCAGAA
AAATATCAAGGGAGTGAAAGCACGATTTGTTGTGACTGATGGTGGGATTACCAGAGTTTAT
CCCAAAGAGGCTGGAGAAAATTGGCAAGAAAACCCAGAGACATATGAGGACAGCTTCTATA
AAAGGAGCCTAGATAATGATAACTATGTTTTCACTGCTCCCTACTTTAACAAAAGTGGACC
TGGTGCCTATGAATCGGGCATTATGGTAAGCAAAGCTGTAGAAATATATATTCAAGGGAAA
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CGTAATGGATTGTGTGATTCTGGATGATGGTGGGTTTCTTCTGATGGCAAATCATGATGAT
TATACTAATCAGATTGGAAGATTTTTTGGAGAGATTGATCCCAGCTTGATGAGACACCTGG
TTAATATATCAGTTTATGCTTTTAACAAATCTTATGATTATCAGTCAGTATGTGAGCCCGG
TGCTGCACCAAAACAAGGAGCAGGACATCGCTCAGCATATGTGCCATCAGTAGCAGACATA
TTACAAATTGGCTGGTGGGCCACTGCTGCTGCCTGGTCTATTCTACAGCAGTTTCTCTTGA
GTTTGACCTTTCCACGACTCCTTGAGGCAGTTGAGATGGAGGATGATGACTTCACGGCCTC
CCTGTCCAAGCAGAGCTGCATTACTGAACAAACCCAGTATTTCTTCGATAACGACAGTAAA
TCATTCAGTGGTGTATTAGACTGTGGAAACTGTTCCAGAATCTTTCATGGAGAAAAGCTTA
TGAACACCAACTTAATATTCATAATGGTTGAGAGCAAAGGGACATGTCCATGTGACACACG
ACTGC

11 - human nucleotide sequence

ATGGCTGCTGGCTGCCTGCTGGCCTTGACTCTGACACTTTTCCAATCTTTGCTCATCGGCC
CCTCGTCGGAGGAGCCGTTCCCTTCGGCCGTCACTATCAAATCATGGGTGGATAAGATGCA

AGAAGACCTTGTCACACTGGCAAAAACAGCAAGTGGAGTCAATCAGCTTGTTGATATTTAT
GAGAAATATCAAGATTTGTATACTGTGGAACCAAATAATGCACGCCAGCTGGTAGAAATTG
CAGCCAGGGATATTGAGAAACTTCTGAGCAACAGATCTAAAGCCCTGGTGAGCCTGGCATT
GGAAGCGGAGAAAGTTCAAGCAGCTCACCAGTGGAGAGAAGATTTTGCAAGCAATGAAGTT
GTCTACTACAATGCAAAGGATGATCTCGATCCTGAGAAAAATGACAGTGAGCCAGGCAGCC
AGAGGATAAAACCTGTTTTCATTGAAGATGCTAATTTTGGACGACAAATATCTTATCAGCA
CGCAGCAGTCCATATTCCTACTGACATCTATGAGGGCTCAACAATTGTGTTAAATGAACTC
AACTGGACAAGTGCCTTAGATGAAGTTTTCAAAAAGAATCGCGAGGAAGACCCTTCATTAT
TGTGGCAGGTTTTTGGCAGTGCCACTGGCCTAGCTCGATATTATCCAGCTTCACCATGGGT
TGATAATAGTAGAACTCCAAATAAGATTGACCTTTATGATGTACGCAGAAGACCATGGTAC
ATCCAAGGAGCTGCATCTCCTAAAGACATGCTTATTCTGGTGGATGTGAGTGGAAGTGTTA
GTGGATTGACACTTAAACTGATCCGAACATCTGTCTCCGAAATGTTAGAAACCCTCTCAGA
TGATGATTTCGTGAATGTAGCTTCATTTAACAGCAATGCTCAGGATGTAAGCTGTTTTCAG
CACCTTGTCCAAGCAAATGTAAGAAATAAAAAAGTGTTGAAAGACGCGGTGAATAATATCA
CAGCCAAAGGAATTACAGATTATAAGAAGGGCTTTAGTTTTGCTTTTGAACAGCTGCTTAA
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GAGAGAGCCCAGGAGATATTTAACAAATACAATAAAGATAAAAAAGTACGTGTATTCAGGT
TTTCAGTTGGTCAACACAATTATGAGAGAGGACCTATTCAGTGGATGGCCTGTGAAAACAA
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GATGTTTTGGGAAGACCAATGGTTTTAGCAGGAGACAAAGCTAAGCAAGTCCAATGGACAA
ATGTGTACCTGGATGCATTGGAACTGGGACTTGTCATTACTGGAACTCTTCCGGTCTTCAA
CATAACCGGCCAATTTGAAAATAAGACAAACTTAAAGAACCAGCTGATTCTTGGTGTGATG
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GAGTCTTGCTTGATGCAGGCTTTACAAATGAACTTGTCCAAAATTACTGGAGTAAGCAGAA
AAATATCAAGGGAGTGAAAGCACGATTTGTTGTGACTGATGGTGGGATTACCAGAGTTTAT
CCCAAAGAGGCTGGAGAAAATTGGCAAGAAAACCCAGAGACATATGAGGACAGCTTCTATA
AAAGGAGCCTAGATAATGATAACTATGTTTTCACTGCTCCCTACTTTAACAAAAGTGGACC
TGGTGCCTATGAATCGGGCATTATGGTAAGCAAAGCTGTAGAAATATATATTCAAGGGAAA
CTTCTTAAACCTGCAGTTGTTGGAATTAAAATTGATGTAAATTCCTGGATAGAGAATTTCA
CCAAAACCTCAATCAGAGATCCGTGTGCTGGTCCAGTTTGTGACTGCAAAAGAAACAGTGA
CGTAATGGATTGTGTGATTCTGGATGATGGTGGGTTTCTTCTGATGGCAAATCATGATGAT
TATACTAATCAGATTGGAAGATTTTTTGGAGAGATTGATCCCAGCTTGATGAGACACCTGG
TTAATATATCAGTTTATGCTTTTAACAAATCTTATGATTATCAGTCAGTATGTGAGCCCGG
TGCTGCACCAAAACAAGGAGCAGGACATCGCTCAGCATATGTGCCATCAGTAGCAGACATA
TTACAAATTGGCTGGTGGGCCACTGCTGCTGCCTGGTCTATTCTACAGCAGTTTCTCTTGA
GTTTGACCTTTCCACGACTCCTTGAGGCAGTTGAGATGGAGGATGATGACTTCACGGCCTC
CCTGTCCAAGCAGAGCTGCATTACTGAACAAACCCAGTATTTCTTCGATAACGACAGTAAA
TCATTCAGTGGTGTATTAGACTGTGGAAACTGTTCCAGAATCTTTCATGGAGAAAAGCTTA
TGAACACCAACTTAATATTCATAATGGTTGAGAGCAAAGGGACATGTCCATGTGACACACG
ACTGCTCATACAAGCGGAGCAGACTTCTGACGGTCCAAATCCTTGTGACATGGTTAAGC

12 - human nucleotide sequence

ATGGCTGCTGGCTGCCTGCTGGCCTTGACTCTGACACTTTTCCAATCTTTGCTCATCGGCC
CCTCGTCGGAGGAGCCGTTCCCTTCGGCCGTCACTATCAAATCATGGGTGGATAAGATGCA
AGAAGACCTTGTCACACTGGCAAAAACAGCAAGTGGAGTCAATCAGCTTGTTGATATTTAT
GAGAAATATCAAGATTTGTATACTGTGGAACCAAATAATGCACGCCAGCTGGTAGAAATTG
CAGCCAGGGATATTGAGAAACTTCTGAGCAACAGATCTAAAGCCCTGGTGAGCCTGGCATT
GGAAGCGGAGAAAGTTCAAGCAGCTCACCAGTGGAGAGAAGATTTTGCAAGCAATGAAGTT
GTCTACTACAATGCAAAGGATGATCTCGATCCTGAGAAAAATGACAGTGAGCCAGGCAGCC
AGAGGATAAAACCTGTTTTCATTGAAGATGCTAATTTTGGACGACAAATATCTTATCAGCA
CGCAGCAGTCCATATTCCTACTGACATCTATGAGGGCTCAACAATTGTGTTAAATGAACTC
AACTGGACAAGTGCCTTAGATGAAGTTTTCAAAAAGAATCGCGAGGAAGACCCTTCATTAT
TGTGGCAGGTTTTTGGCAGTGCCACTGGCCTAGCTCGATATTATCCAGCTTCACCATGGGT
TGATAATAGTAGAACTCCAAATAAGATTGACCTTTATGATGTACGCAGAAGACCATGGTAC
ATCCAAGGAGCTGCATCTCCTAAAGACATGCTTATTCTGGTGGATGTGAGTGGAAGTGTTA

GTGGATTGACACTTAAACTGATCCGAACATCTGTCTCCGAAATGTTAGAAACCCTCTCAGA
TGATGATTTCGTGAATGTAGCTTCATTTAACAGCAATGCTCAGGATGTAAGCTGTTTTCAG
CACCTTGTCCAAGCAAATGTAAGAAATAAAAAAGTGTTGAAAGACGCGGTGAATAATATCA
CAGCCAAAGGAATTACAGATTATAAGAAGGGCTTTAGTTTTGCTTTTGAACAGCTGCTTAA
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ATGTGTACCTGGATGCATTGGAACTGGGACTTGTCATTACTGGAACTCTTCCGGTCTTCAA
CATAACCGGCCAATTTGAAAATAAGACAAACTTAAAGAACCAGCTGATTCTTGGTGTGATG
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TTAATATATCAGTTTATGCTTTTAACAAATCTTATGATTATCAGTCAGTATGTGAGCCCGG
TGCTGCACCAAAACAAGGAGCAGGACATCGCTCAGCATATGTGCCATCAGTAGCAGACATA

TTACAAATTGGCTGGTGGGCCACTGCTGCTGCCTGGTCTATTCTACAGCAGTTTCTCTTGA
GTTTGACCTTTCCACGACTCCTTGAGGCAGTTGAGATGGAGGATGATGACTTCACGGCCTC
CCTGTCCAAGCAGAGCTGCATTACTGAACAAACCCAGTATTTCTTCGATAACGACAGTAAA
TCATTCAGTGGTGTATTAGACTGTGGAAACTGTTCCAGAATCTTTCATGGAGAAAAGCTTA
TGAACACCAACTTAATATTCATAATGGTTGAGAGCAAAGGGACATGTCCATGTGACACACG
ACTGCTCATACAAGCGGAGCAGACTTCTGACGGTCCAAATCCTTGTGACATGGTTAAGCAA
CCTAGATACCGAAAAGGGCCTGATGTCTGCTTTGATAACAATGTCTTGGAGGATTATACTG
ACTGTGGTGGTGTTTCTG

13 - human amino acid sequence

MAAGCLLALTLTLFQSLLIGPSSEEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVSLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIEDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL
NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE
ERAQEIFNKYNKDKKVRVFRFSVGQHNYERGPIQWMACENKGYYYEIPSIGAIRINTQEYL
DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQFENKTNLKNQLILGVM
GVDVSLEDIKRLTPRFTLCPNGYYFAIDPNGYVLLHPNLQPKNPKSQEPVTLDFLDAELEN
DIKVEIRNKMIDGESGEKTFRTLVKSQDERYIDKGNRTYTWTPVNGTDYSLALVLPTYSFY
YIKAKLEETITQARSKKGKMKDSETLKPDNFEESGYTFIAPRDYCNDLKISDNNTEFLLNF
NEFIDRKTPNNPSCNADLINRVLLDAGFTNELVQNYWSKQKNIKGVKARFVVTDGGITRVY
PKEAGENWQENPETYEDSFYKRSLDNDNYVFTAPYFNKSGPGAYESGIMVSKAVEIYIQGK
LLKPAVVGIKIDVNSWIENFTKTSIRDPCAGPVCDCKRNSDVMDCVILDDGGFLLMANHDD
YTNQIGRFFGEIDPSLMRHLVNISVYAFNKSYDYQSVCEPGAAPKQGAGHRSAYVPSVADI
LQIGWWATAAAWSILQQFLLSLTFPRLLEAVEMEDDDFTASLSKQSCITEQTQYFFDNDSK
SFSGVLDCGNCSRIFHGEKLMNTNLIFIMVESKGTCPCDTRL

14 - human amino acid sequence

MAAGCLLALTLTLFQSLLIGPSSEEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVSLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIEDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL

NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE
ERAQEIFNKYNKDKKVRVFRFSVGQHNYERGPIQWMACENKGYYYEIPSIGAIRINTQEYL
DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQFENKTNLKNQLILGVM
GVDVSLEDIKRLTPRFTLCPNGYYFAIDPNGYVLLHPNLQPKNPKSQEPVTLDFLDAELEN
DIKVEIRNKMIDGESGEKTFRTLVKSQDERYIDKGNRTYTWTPVNGTDYSLALVLPTYSFY
YIKAKLEETITQARSKKGKMKDSETLKPDNFEESGYTFIAPRDYCNDLKISDNNTEFLLNF
NEFIDRKTPNNPSCNADLINRVLLDAGFTNELVQNYWSKQKNIKGVKARFVVTDGGITRVY
PKEAGENWQENPETYEDSFYKRSLDNDNYVFTAPYFNKSGPGAYESGIMVSKAVEIYIQGK
LLKPAVVGIKIDVNSWIENFTKTSIRDPCAGPVCDCKRNSDVMDCVILDDGGFLLMANHDD
YTNQIGRFFGEIDPSLMRHLVNISVYAFNKSYDYQSVCEPGAAPKQGAGHRSAYVPSVADI
LQIGWWATAAAWSILQQFLLSLTFPRLLEAVEMEDDDFTASLSKQSCITEQTQYFFDNDSK
SFSGVLDCGNCSRIFHGEKLMNTNLIFIMVESKGTCPCDTRLLIQAEQTSDGPNPCDMVK

15 - human amino acid sequence

MAAGCLLALTLTLFQSLLIGPSSEEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVSLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIEDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL
NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE
ERAQEIFNKYNKDKKVRVFRFSVGQHNYERGPIQWMACENKGYYYEIPSIGAIRINTQEYL
DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQFENKTNLKNQLILGVM
GVDVSLEDIKRLTPRFTLCPNGYYFAIDPNGYVLLHPNLQPKNPKSQEPVTLDFLDAELEN
DIKVEIRNKMIDGESGEKTFRTLVKSQDERYIDKGNRTYTWTPVNGTDYSLALVLPTYSFY
YIKAKLEETITQARSKKGKMKDSETLKPDNFEESGYTFIAPRDYCNDLKISDNNTEFLLNF
NEFIDRKTPNNPSCNADLINRVLLDAGFTNELVQNYWSKQKNIKGVKARFVVTDGGITRVY
PKEAGENWQENPETYEDSFYKRSLDNDNYVFTAPYFNKSGPGAYESGIMVSKAVEIYIQGK
LLKPAVVGIKIDVNSWIENFTKTSIRDPCAGPVCDCKRNSDVMDCVILDDGGFLLMANHDD
YTNQIGRFFGEIDPSLMRHLVNISVYAFNKSYDYQSVCEPGAAPKQGAGHRSAYVPSVADI
LQIGWWATAAAWSILQQFLLSLTFPRLLEAVEMEDDDFTASLSKQSCITEQTQYFFDNDSK

SFSGVLDCGNCSRIFHGEKLMNTNLIFIMVESKGTCPCDTRLLIQAEQTSDGPNPCDMVKQ
PRYRKGPDVCFDNNVLEDYTDCGGVS

16 - human alpha2 delta-1 amino acid sequence

MAAGCLLALTLTLFQSLLIGPSSEEPFPSAVTIKSWVDKMQEDLVTLAKTASGVNQLVDIY
EKYQDLYTVEPNNARQLVEIAARDIEKLLSNRSKALVSLALEAEKVQAAHQWREDFASNEV
VYYNAKDDLDPEKNDSEPGSQRIKPVFIEDANFGRQISYQHAAVHIPTDIYEGSTIVLNEL
NWTSALDEVFKKNREEDPSLLWQVFGSATGLARYYPASPWVDNSRTPNKIDLYDVRRRPWY
IQGAASPKDMLILVDVSGSVSGLTLKLIRTSVSEMLETLSDDDFVNVASFNSNAQDVSCFQ
HLVQANVRNKKVLKDAVNNITAKGITDYKKGFSFAFEQLLNYNVSRANCNKIIMLFTDGGE
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DVLGRPMVLAGDKAKQVQWTNVYLDALELGLVITGTLPVFNITGQFENKTNLKNQLILGVM
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CLAIMS:

1. A method for the screening of ligands which bind a cerebral cortical voltage-dependent calcium channel $\alpha_2\delta$-1 subunit, said method comprising the steps of:

- contacting a secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide with:
  - a ligand of interest; and
  - a labelled compound which binds the $\alpha_2\delta$-1 subunit; and
- measuring the level of binding of the labelled compound to the $\alpha_2\delta$-1 subunit.

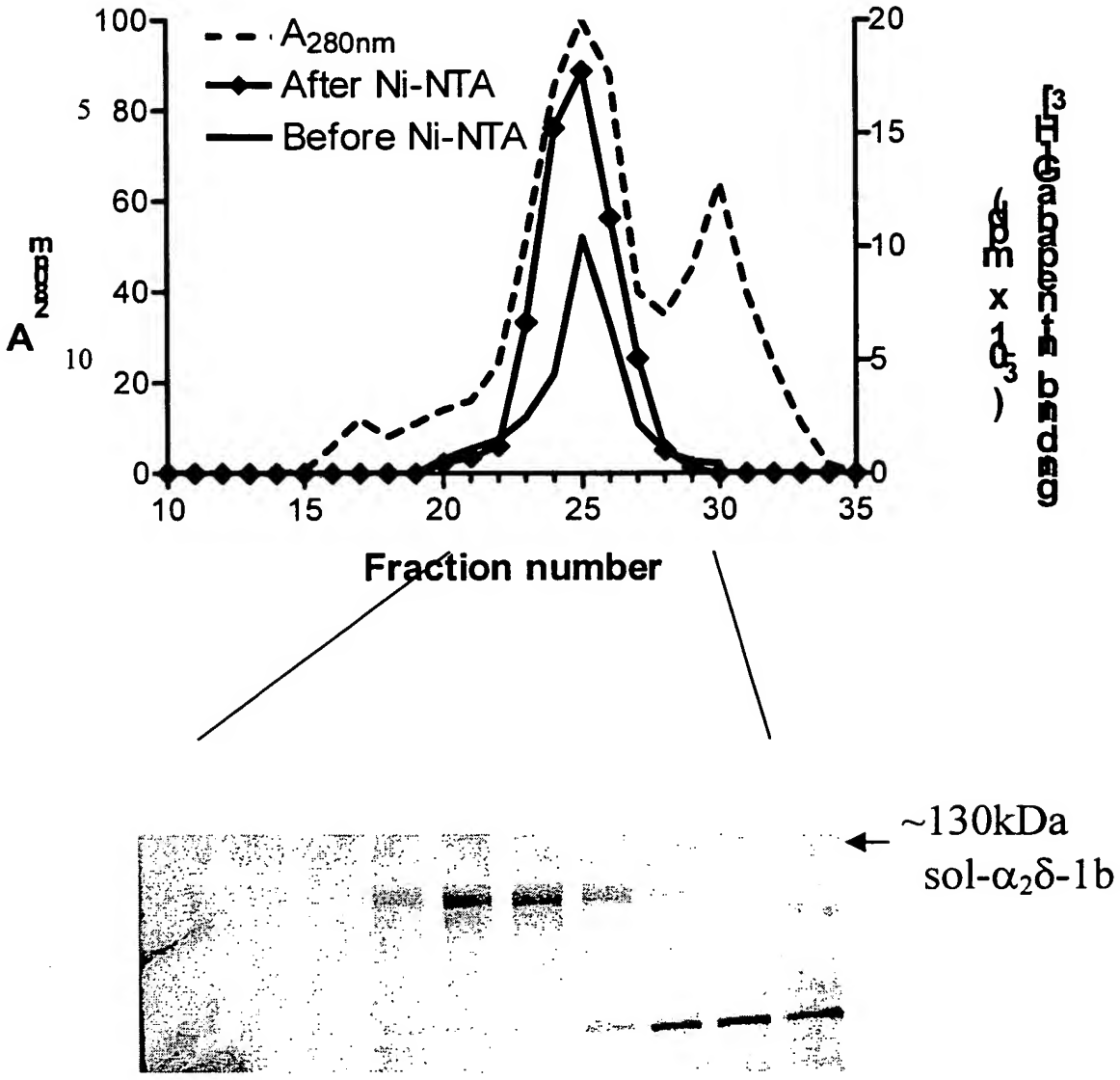
2. A method according to claim 1, wherein said contacting and said binding is in a well of a flashplate.

3. A method according to claim 1, wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide is selected from the group consisting of SEQ ID NO: 6, 7, 8, 9, 13, 14 and 15.

4. A method according to claim 1, wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide is selected from the group consisting of SEQ ID NO: 9 and 15.

5. A method according to claim 1, wherein said secreted soluble recombinant calcium channel $\alpha_2\delta$-1 subunit polypeptide is SEQ ID NO: 9.

FIGURE 1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After Ni-NTA
Before Ni-NTA
Fraction number
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sol-α2δ-1b

FIGURE 2

SPA assay of [^{3}H]gabapentin (18.4nM) binding to s-$\alpha_2\delta$-1b-6His (20µl). Optimis
Imidazole concentration in the assay.

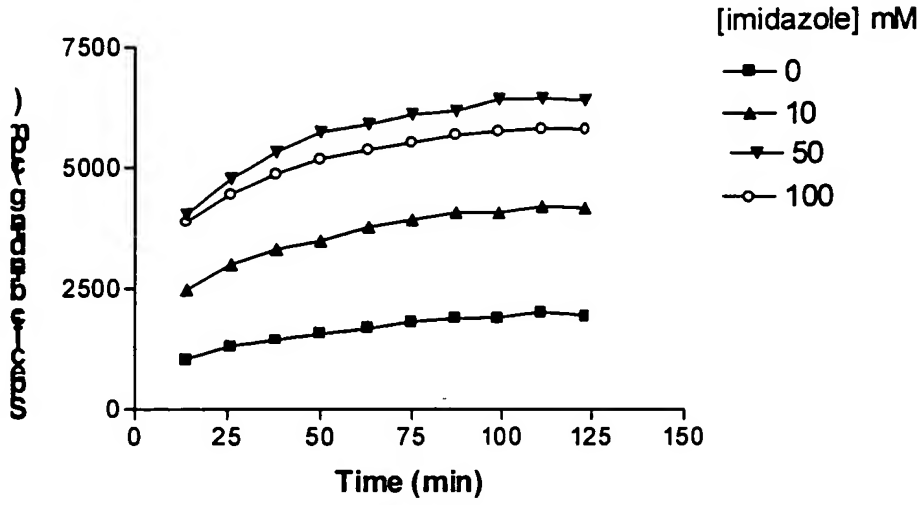


FIGURE 3

Flashplate assay of [^{3}H]gabapentin (14nM) binding to s-$\alpha_2\delta$-1b-6His (10µl). Optimisation of Imidazole concentration in the assay.

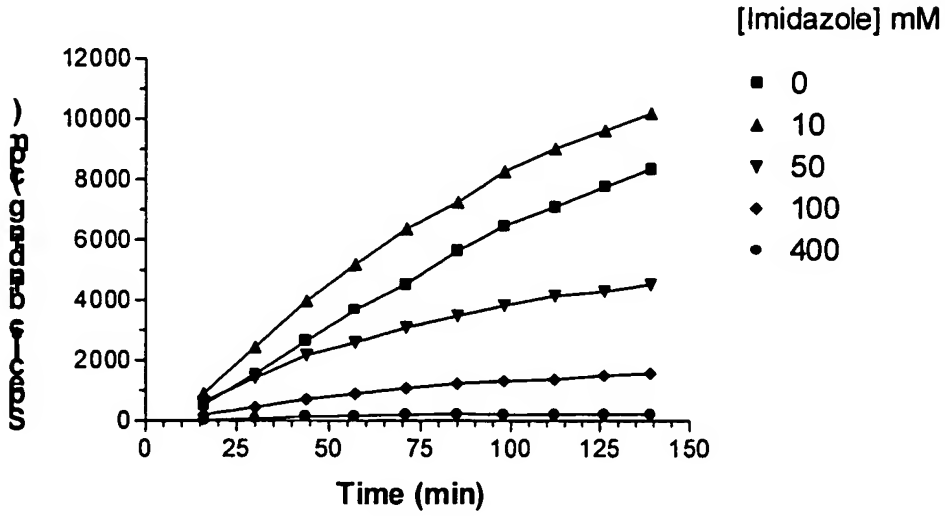
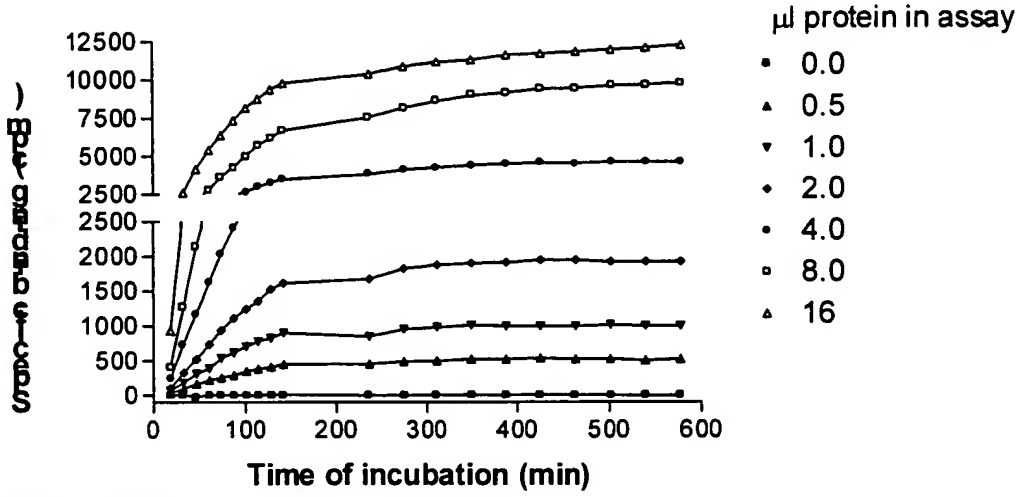


FIGURE 4

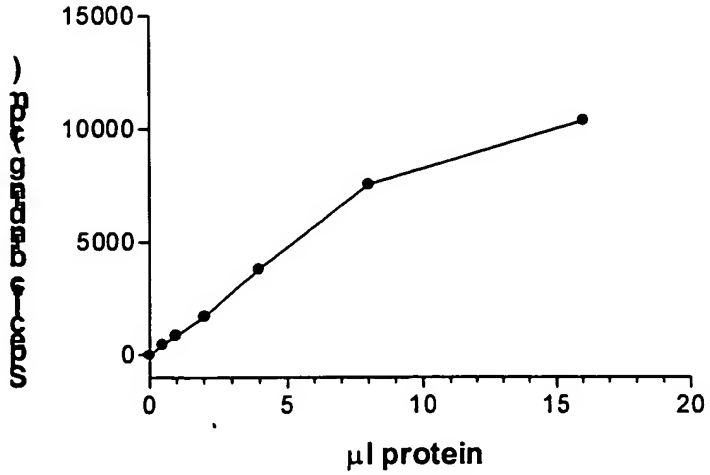
Flashplate time course of [^{3}H]gabapentin (13nM) binding to various concentrations of s-$\alpha_2\delta$-1b-6His.



10mM imidazole in assay

FIGURE 5

Determination of s-$\alpha_2\delta$-1b-6His capacity of flashplate assay. Counted after 3hour incubation



Utility Application

FIGURE 6

Determination of the optimum imidazole concentration required to maximize the [^{3}H]gabapentin (13nM) binding window using a constant amount of purified s-$\alpha_2\delta$-1b-6His (2µl). Assayed after 3hour incubation.

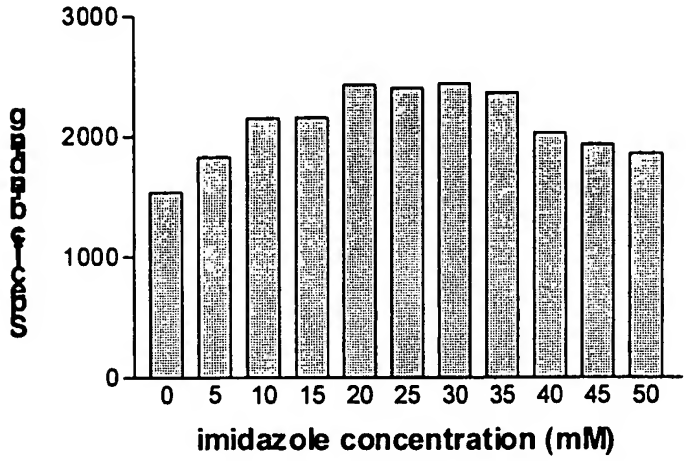
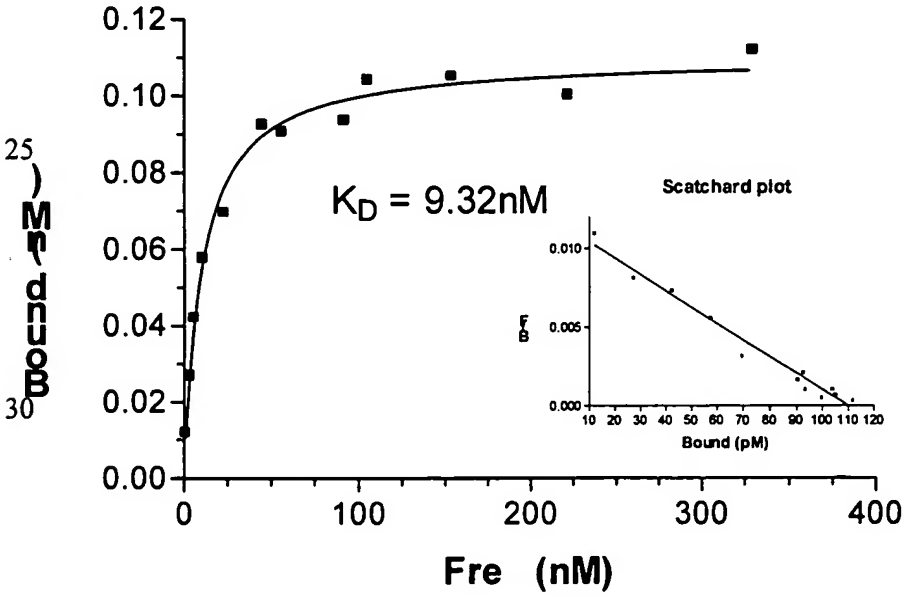


FIGURE 7

Flashplate assay of [^{3}H]gabapentin saturation binding to purified s-$\alpha_2\delta$-1b-6His. Assayed after three hour incubation (see table 1 for details).



Utility Application

Figure 8

Flashplate time course optimisation of Imidazole concentration required to maximize the [^{3}H]Leucine (10.1nM) binding window to s-$\alpha_2\delta$-1b-6His. Assayed after three hour incubation.

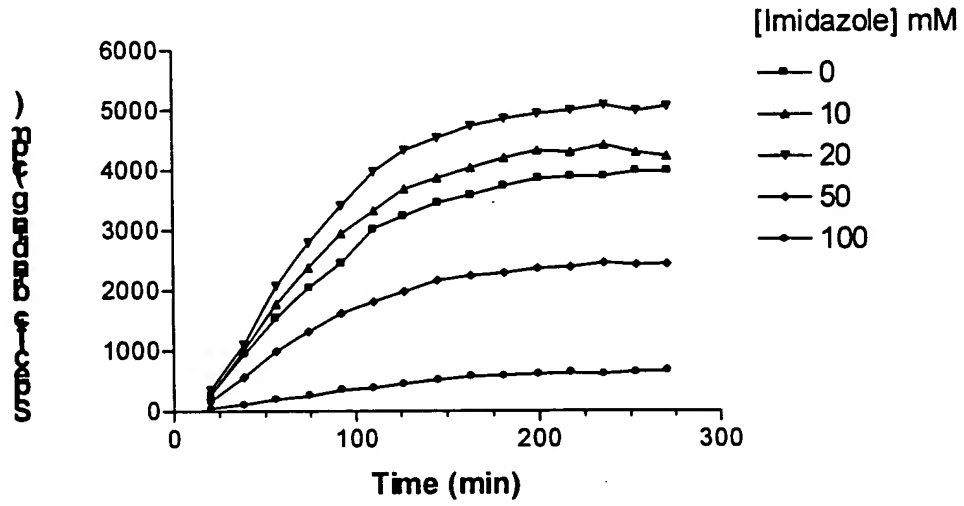
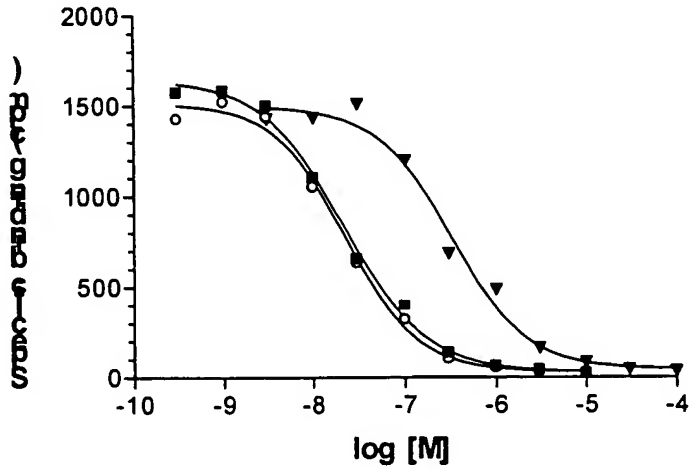


FIGURE 9

Competition curves of three compounds in the flashplate assay format (see table 2 for details). Assayed after 3 hour incubation.



- ■ Gabapentin
- ○ (S+)-3-isobutyl GABA
- ▼ (R-)-3-isobutyl GABA

ABSTRACT

Method for the screening of $\alpha_2\delta$-1 subunit binding ligands

A method for the screening of ligands which bind to soluble $\alpha_2\,\delta$-1 subtype polypeptides.

A0000179-C1-66-MG

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT	: Francois Bertelli et al	EXAMINER	:
SERIAL NO.	:	ART UNIT	:
FILED	: Herewith	PAPER NO	:

FOR : Method For The Screening of Alpha2Delta Subunit Binding Ligands

Request for Transfer of Computer Readable Form Under 37 CFR 1.821(e)

March 6, 2002

Commissioner for Patent
Washington, D.C. 20231

Dear Sir:

The paper copy of the Sequence Listing in this application, is identical to the computer readable copy of the Sequence Listing filed in Application No. 09/397,549, Filed September 16, 1999. In accordance with 37CFR 1.821(e), please use the only filed computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make necessary change in the application number and filing date for the instant application. A paper copy of the Sequence Listing is included in the originally filed specification of the instant application.

Respectfully submitted,

Dated: March 6, 2002

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Facsimile: (734) 622-1553

EXPRESS MAIL NO. EJ054450643US
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35 40 45

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Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
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Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                 85                  90                  95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
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Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
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Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
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Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
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Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
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Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
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Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
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Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
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Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
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Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
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Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
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Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
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Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
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Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
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Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
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Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
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Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
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Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
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Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
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Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
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Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
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Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

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Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
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Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
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Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
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Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
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Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Ala Leu Glu Asp Tyr
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Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu Trp Ser Ile
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Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
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Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
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Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                 85                  90                  95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
             100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
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Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
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Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
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Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
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Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
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Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
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Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
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Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
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Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
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Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
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Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
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Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
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Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
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Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
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Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
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Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
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Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
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Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
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Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
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Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
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Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
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Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
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Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
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Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
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Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
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Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
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Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
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Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu
1010 1015

<210> 7
<211> 1036
<212> PRT
<213> Sus scrofa

<400> 7
Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
1 5 10 15

Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
20 25 30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
245 250 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
260 265 270

```
Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
                325                 330                 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385                 390                 395                 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
                405                 410                 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
            420                 425                 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
        435                 440                 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
    450                 455                 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465                 470                 475                 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
                485                 490                 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
            500                 505                 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
        515                 520                 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
    530                 535                 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545                 550                 555                 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
                565                 570                 575
```

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

```
Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
                885                 890                 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
            900                 905                 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
        915                 920                 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys
1025                1030                1035
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<210> 8
<211> 1063
<212> PRT
<213> Sus scrofa

<400> 8

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Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
  1               5                  10                  15

Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
            20                  25                  30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
        35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
    50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                85                  90                  95
```

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Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
                325                 330                 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385                 390                 395                 400
```

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
900 905 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
930 935 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945 950 955 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
965 970 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
980 985 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005

```
Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025                1030                1035                1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Ala Leu Glu Asp Tyr
                1045                1050                1055

Thr Asp Cys Gly Gly Val Ser
           1060
```

<210> 9
<211> 1069
<212> PRT
<213> Sus scrofa

<400> 9

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Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
  1               5                  10                  15

Leu Leu Ile Gly Pro Ser Ser Gln Glu Pro Phe Pro Ser Ala Val Thr
             20                  25                  30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
         35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
     50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                 85                  90                  95

Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Asp Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
```

```
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala S r Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
                325                 330                 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365

Ala Gln Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Thr Phe Ser Val Gly Gln His Asn Tyr Asp Arg Gly Pro Ile Gln
385                 390                 395                 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
                405                 410                 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
            420                 425                 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
        435                 440                 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
    450                 455                 460

Pro Val Phe Asn Ile Thr Gly Gln Asn Glu Asn Lys Thr Asn Leu Lys
465                 470                 475                 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
                485                 490                 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
```

```
            500                 505                 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
        515                 520                 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
    530                 535                 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545                 550                 555                 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
                565                 570                 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
            580                 585                 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
        595                 600                 605

Phe Tyr Tyr Ile Lys Ala Lys Ile Glu Glu Thr Ile Thr Gln Ala Arg
    610                 615                 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625                 630                 635                 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
                645                 650                 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
            660                 665                 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
        675                 680                 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
    690                 695                 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705                 710                 715                 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
                725                 730                 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
            740                 745                 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
        755                 760                 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
    770                 775                 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785                 790                 795                 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
```

```
                805                 810                 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
            820                 825                 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
        835                 840                 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
    850                 855                 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865                 870                 875                 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
                885                 890                 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Ile
            900                 905                 910

Ala Asp Ile Leu His Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
        915                 920                 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Val Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asp Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025                1030                1035                1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Ala Leu Glu Asp Tyr
                1045                1050                1055

Thr Asp Cys Gly Gly Val Ser His His His His His His
            1060                1065
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<212> DNA
<213> Homo sapiens

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caagaagacc ttgtcacact ggcaaaaaca gcaagtggag tcaatcagct tgttgatatt 180
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gccttggtat taccaaccta cagtttttac tatataaaag ccaaactaga agagacaata 1860
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35 40 45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65 70 75 80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100 105 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
130 135 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145 150 155 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
180 185 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
195 200 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
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Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile

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Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
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Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
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Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
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Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
385                 390                 395                 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
                405                 410                 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
            420                 425                 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
        435                 440                 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
    450                 455                 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465                 470                 475                 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
                485                 490                 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
            500                 505                 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
        515                 520                 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
    530                 535                 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
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Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly

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    850                 855                 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865                 870                 875                 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
                885                 890                 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
            900                 905                 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
        915                 920                 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
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Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu
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Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
         35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
     50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
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Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
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Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
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Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
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Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
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Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
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Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
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Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
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Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
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Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
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Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
            420                 425                 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
        435                 440                 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
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Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465                 470                 475                 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
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Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
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Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
        515                 520                 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
    530                 535                 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545                 550                 555                 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
                565                 570                 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
            580                 585                 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
        595                 600                 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
    610                 615                 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625                 630                 635                 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
                645                 650                 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
            660                 665                 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
        675                 680                 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
    690                 695                 700
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Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
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Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
                725                 730                 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
            740                 745                 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
        755                 760                 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
    770                 775                 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785                 790                 795                 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
                805                 810                 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
            820                 825                 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
        835                 840                 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
    850                 855                 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865                 870                 875                 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
                885                 890                 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
            900                 905                 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
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Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
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Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005
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Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
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<212> PRT
<213> Homo sapiens

<400> 15

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Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
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Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
             20                  25                  30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
         35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
     50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
 65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                 85                  90                  95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220
```

```
Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
                325                 330                 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
            340                 345                 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
        355                 360                 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
    370                 375                 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
385                 390                 395                 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
                405                 410                 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
            420                 425                 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
        435                 440                 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
    450                 455                 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465                 470                 475                 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
                485                 490                 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
            500                 505                 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
        515                 520                 525
```

```
Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
    530                 535                 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545                 550                 555                 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
                565                 570                 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
            580                 585                 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
        595                 600                 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
    610                 615                 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
625                 630                 635                 640

Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
                645                 650                 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
            660                 665                 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
        675                 680                 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
    690                 695                 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705                 710                 715                 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
                725                 730                 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
            740                 745                 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
        755                 760                 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
    770                 775                 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785                 790                 795                 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
                805                 810                 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
            820                 825                 830
```

```
Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
        835                 840                 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
    850                 855                 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865                 870                 875                 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
                885                 890                 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
            900                 905                 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
        915                 920                 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025                1030                1035                1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr
                1045                1050                1055

Thr Asp Cys Gly Gly Val Ser
            1060
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<210> 16
<211> 1091
<212> PRT
<213> Homo sapiens

<400> 16

```
Met Ala Ala Gly Cys Leu Leu Ala Leu Thr Leu Thr Leu Phe Gln Ser
  1               5                  10                  15

Leu Leu Ile Gly Pro Ser Ser Glu Glu Pro Phe Pro Ser Ala Val Thr
```

```
            20                  25                  30

Ile Lys Ser Trp Val Asp Lys Met Gln Glu Asp Leu Val Thr Leu Ala
        35                  40                  45

Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
    50                  55                  60

Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Gln Leu Val Glu
65                  70                  75                  80

Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
                85                  90                  95

Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
            100                 105                 110

Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
        115                 120                 125

Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gln Arg
    130                 135                 140

Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Arg Gln Ile Ser
145                 150                 155                 160

Tyr Gln His Ala Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
                165                 170                 175

Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
            180                 185                 190

Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Trp Gln Val Phe
        195                 200                 205

Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
    210                 215                 220

Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225                 230                 235                 240

Arg Pro Trp Tyr Ile Gln Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
                245                 250                 255

Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Ile
            260                 265                 270

Arg Thr Ser Val Ser Glu Met Leu Glu Thr Leu Ser Asp Asp Asp Phe
        275                 280                 285

Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
    290                 295                 300

Gln His Leu Val Gln Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305                 310                 315                 320

Ala Val Asn Asn Ile Thr Ala Lys Gly Ile Thr Asp Tyr Lys Lys Gly
```

325 330 335

Phe Ser Phe Ala Phe Glu Gln Leu Leu Asn Tyr Asn Val Ser Arg Ala
340 345 350

Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg
355 360 365

Ala Gln Glu Ile Phe Asn Lys Tyr Asn Lys Asp Lys Lys Val Arg Val
370 375 380

Phe Arg Phe Ser Val Gly Gln His Asn Tyr Glu Arg Gly Pro Ile Gln
385 390 395 400

Trp Met Ala Cys Glu Asn Lys Gly Tyr Tyr Tyr Glu Ile Pro Ser Ile
405 410 415

Gly Ala Ile Arg Ile Asn Thr Gln Glu Tyr Leu Asp Val Leu Gly Arg
420 425 430

Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gln Val Gln Trp Thr Asn
435 440 445

Val Tyr Leu Asp Ala Leu Glu Leu Gly Leu Val Ile Thr Gly Thr Leu
450 455 460

Pro Val Phe Asn Ile Thr Gly Gln Phe Glu Asn Lys Thr Asn Leu Lys
465 470 475 480

Asn Gln Leu Ile Leu Gly Val Met Gly Val Asp Val Ser Leu Glu Asp
485 490 495

Ile Lys Arg Leu Thr Pro Arg Phe Thr Leu Cys Pro Asn Gly Tyr Tyr
500 505 510

Phe Ala Ile Asp Pro Asn Gly Tyr Val Leu Leu His Pro Asn Leu Gln
515 520 525

Pro Lys Asn Pro Lys Ser Gln Glu Pro Val Thr Leu Asp Phe Leu Asp
530 535 540

Ala Glu Leu Glu Asn Asp Ile Lys Val Glu Ile Arg Asn Lys Met Ile
545 550 555 560

Asp Gly Glu Ser Gly Glu Lys Thr Phe Arg Thr Leu Val Lys Ser Gln
565 570 575

Asp Glu Arg Tyr Ile Asp Lys Gly Asn Arg Thr Tyr Thr Trp Thr Pro
580 585 590

Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser
595 600 605

Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Glu Thr Ile Thr Gln Ala Arg
610 615 620

Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn

625 630 635 640

Phe Glu Glu Ser Gly Tyr Thr Ph Ile Ala Pro Arg Asp Tyr Cys Asn
645 650 655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
660 665 670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp
675 680 685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Asn Glu Leu Val
690 695 700

Gln Asn Tyr Trp Ser Lys Gln Lys Asn Ile Lys Gly Val Lys Ala Arg
705 710 715 720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
725 730 735

Gly Glu Asn Trp Gln Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
740 745 750

Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Pro Tyr Phe
755 760 765

Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
770 775 780

Ala Val Glu Ile Tyr Ile Gln Gly Lys Leu Leu Lys Pro Ala Val Val
785 790 795 800

Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr
805 810 815

Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
820 825 830

Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu
835 840 845

Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly
850 855 860

Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
865 870 875 880

Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala
885 890 895

Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val
900 905 910

Ala Asp Ile Leu Gln Ile Gly Trp Trp Ala Thr Ala Ala Ala Trp Ser
915 920 925

Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu

```
    930                 935                 940

Ala Val Glu Met Glu Asp Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln
945                 950                 955                 960

Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys
                965                 970                 975

Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
            980                 985                 990

Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
        995                1000                1005

Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Gln Ala Glu Gln
   1010                1015                1020

Thr Ser Asp Gly Pro Asn Pro Cys Asp Met Val Lys Gln Pro Arg Tyr
1025                1030                1035                1040

Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr
                1045                1050                1055

Thr Asp Cys Gly Gly Val Ser Gly Leu Asn Pro Ser Leu Trp Tyr Ile
            1060                1065                1070

Ile Gly Ile Gln Phe Leu Leu Leu Trp Leu Val Ser Gly Ser Thr His
       1075                1080                1085

Arg Leu Leu
   1090
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<210> 17
<211> 3600
<212> DNA
<213> Homo sapiens

<400> 17

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gcaaaatcct atacgtgtcc tctattggaa aatttgggcg tttgttgttg cattgttggt 3600

<210> 18
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 18
ggggattgat cttcgatcgc g 21

<210> 19
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 19
ctgagatttg gggttctttg g 21

<210> 20
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 20
tcgccaccat ggctgctggc tgcctgctg 29

<210> 21
<211> 52
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 21
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